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Volume 234 MAY 23, 1946 Number 21

HEPATOLENTICULAR DEGENERATION*

II. Nutritional Factors: Observations on Methionine and High-Protein Diets

F. HOMBURGER, M.D.†

BOSTON

IN A previous publication,[1] the clinical features and laboratory findings in 4 cases of hepatolenticular degeneration were described. It was pointed out that the patients seemed to benefit from diets intended to protect the liver and that the cephalin-flocculation test was the most sensitive liver-function test available for this disease. The present paper reports the course of 2 of these patients treated by dietary means during periods of observation of fourteen and seventeen months, respectively. There appear to be nutritional factors that alter the course of this disease.

METHOD OF STUDY

The following factors were investigated: the effects of high-calorie, high-protein, high-carbohydrate and low-fat diets; the effects of high-calorie, high-carbohydrate, low-protein and low-fat diets; and the effects of methionine in the presence of hepatic dysfunction.

The patients, who were intelligent and co-operative, were allowed to remain at home during most of this experiment and to pursue their usual occupations. The patient in Case 1 worked as a messenger, and the patient in Case 2 supervised production in his father's medium-sized textile plant. The mother of the first patient provided all his food, and the wife of the second patient, a registered nurse and a trained dietitian, prepared his meals. The food intake of the patients was well controlled by having these reliable persons weigh their food at regular intervals and report the values. The patients were seen about once a week, and the results of therapy were evaluated by clinical examination, by motion-picture records of the tremor and by liver-function tests (cephalin-flocculation tests and prothrombin-time determinations‡).

After trials with various foods, suitable diets were found that could be taken by either patient over prolonged periods of time.§ These basic diets contained the following ingredients: protein, 25 per cent; carbohydrate, 70 per cent; and fat, 5 per cent. The total daily calories were 3690 for the first patient and 3000 for the second patient.

The protein was derived from egg white, cottage cheese, skimmed milk, lean fish, chicken and lean red meat, such as lamb and beef. The patients endeavored to use these same sources of protein in fairly constant proportions by adhering to comparable menus every day. Egg white and sugar in the form of angel cake was found to be helpful in maintaining the high protein and carbohydrate levels of the diet, and mixtures of fruit juices and skimmed-milk powder with Karo syrup added were found to achieve the same purpose. The first patient adhered to the basic diet for over seven months. During the eighth month the fat content was increased to 15 per cent and the carbohydrate content was correspondingly lowered. The protein value was not changed. The second patient continued on the diet for one year. During the thirteenth month he too tripled his fat ration at the expense of the carbohydrate.

The effect of a low-protein diet was studied in Case 1 after the liver function had become normal under the influence of a high-protein diet. The usefulness of methionine for the control of the ensuing liver dysfunction was investigated. For this experiment the patient was in the hospital for six weeks, during which time his food intake was maintained at 4000 calories. The nitrogen balance was determined by the use of tabulated food-nitrogen values, and the urinary nitrogen by the Kjeldahl method. An allowance of 10 per cent of the nitrogen intake was made for fecal loss. Methionine was administered in the form of Meonine‖ tablets in divided doses of 5 gm. daily. The food intake and

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‡The laboratory methods have already been described.[1] The laboratory tests were done by the Surgical Research Laboratory of the Boston City Hospital.

§The co-operation of Miss D. Rubinoff and Mrs. J. Harrison, dietitians is gratefully acknowledged.

‖Meonine was kindly supplied through the courtesy of Drs. R. M. Johnson and P. György of Wyeth, Incorporated, Philadelphia.

administration of methionine were varied as required by the experiment described below. Following this study, methionine was given in similar doses for six weeks.

Although the course of this disease is well known and is always progressive, these studies were controlled by following the sister of the patient represented by Case 1. This woman (M. R. of the previous publication[1]) also suffered from hepatolenticular degeneration but refused dietary measures.

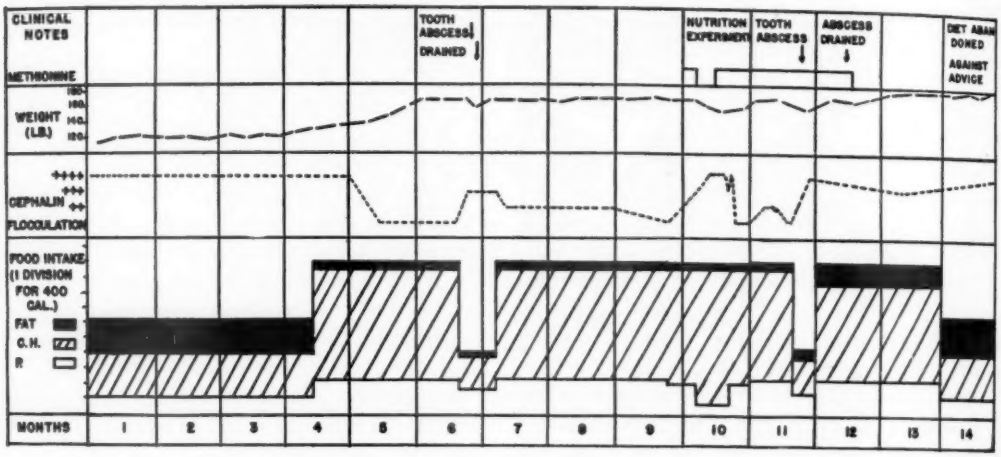

FIGURE 1. *The Course of Case 1.*

This suggests a favorable effect by a high-protein diet and shows the coincidence of a lowered food intake and liver dysfunction. (CH = carbohydrate; P= protein.)

RESULTS

Two groups of observations were made. The first dealt with the patient's general course while on the experimental diet, and the second with findings obtained in the nutritional experiment performed in Case 1 and with the value of methionine in this case.

Clinical Observations on the Effect of Diets

CASE 1. J. R., a 20-year-old man, had had difficulty in writing since the age of 5 and an increasingly severe tremor of the hands. He had two siblings. His brother, an identical twin, died of hepatolenticular degeneration at the age of 18. His sister was also suffering from hepatolenticular degeneration. The parents, who were first cousins, did not have the disease.[1] The patient showed the typical Kayser Fleischer ring of the cornea.

On physical examination the liver and spleen did not seem to be enlarged. The diet previous to the time of this study had consisted of 2400 calories, with 45 per cent carbohydrates, 17 per cent protein and 38 per cent fat. The course on the basic experimental diet from November, 1944, to April, 1945, has been described[1] and is included in Figure 1. The patient's general health improved steadily, and at the end of April, 1945, the cephalin-flocculation reaction was +. In May, 1945, the patient was hospitalized and placed on a low-protein diet, whereupon the cephalin-flocculation reaction became ++++ and the prothrombin concentration 40 per cent of normal. After the liver function had returned to previous levels following the administration of a high-protein diet, an abscess of a molar tooth developed and was drained through the dental pulp. The patient complained of malaise, epigastric discomfort and rectal tenesmus, but x-ray studies of the esophagus, stomach and rectosigmoid were negative. The liver and spleen were of normal size on physical examination, and the spleen was slightly enlarged on x-ray examination. Toward the end of June the cephalin-flocculation reaction was ++++ and the prothrombin concentration was 25 per cent of normal. Five grams of methionine daily was added to the high-protein diet, and after 2 weeks, although the patient had subjectively improved, the cephalin-flocculation reaction remained ++++. The prothrombin time had become normal. During this period dental sepsis was a complicating factor, making the correct interpretation of results most difficult. The infected tooth was removed on July 20, and the improvement continued. Methionine was given for another 4 weeks. The cephalin-flocculation reaction remained +++ or ++++ in spite of subjective improvement. The patient abandoned the high-protein diet in the 14th month of this period of observation, and thereafter his condition deteriorated.

CASE 2. I. S., a 39-year-old man, had suffered from tremor of both hands since 1932. The parents were cousins once removed. His symptoms came on in the course of 1 month and remained stationary, with a slight exacerbation during 1943-1944. This patient had had numerous gastrointestinal upsets in past years and had been accustomed to fatty and spiced food consisting of 2800 calories, with 18 per cent protein, 32 per cent carbohydrate and 50 per cent fat. A diet of 3000 calories with 25 per cent protein, 70 per cent carbohydrates and 5 per cent fat was started in June, 1944 (Fig. 2). In terms of calories this diet was not significantly greater than the one he had been used to. The patient soon improved. The tremor diminished, and skilled acts, hitherto impossible, became feasible. This improvement has continued. The patient, strikingly, has had no more gastrointestinal episodes except some abdominal pain, in one instance following an emotional strain and lasting for 6 hours. The liver-function tests were unchanged. The cephalin-flocculation reaction was ++++ or +++ until September, 1945, when it became +. Motion pictures show a noticeable improvement of the tremor.

The sister of the first patient (M. R.), whose course until February, 1945, has been described,[1] refused dietary therapy and lived on a capricious low food intake. Her tremor was more marked in frequency and amplitude. She had a persistent resting tremor, greatly exaggerated by sustention.

The handwriting did not markedly change, but it was becoming impossible for the patient to carry packages or to hold on to streetcar straps. The corneal ring was wider than on previous occasions. The cephalin-flocculation reaction was ++++, and the prothrombin concentration 65 per cent of normal.

Course following Administration of a Low-Protein Diet and Methionine Therapy

The patient in Case 1 was hospitalized for the purpose of this study. During the first two weeks he was put on a high-protein diet with 35 gm. of nitrogen, and during the second week he received 5 gm. of methionine in tablets divided during the day (Fig. 3). For the next two weeks he was kept on a low-protein diet with not over 10 gm. of nitrogen. The nitrogen balance was re-established on the sixth day of the low-protein period (the nineteenth day of the study). On the same day, the prothrombin concentration was 45 per cent of normal, the cephalin-flocculation reaction, which during the control period had remained at + or ++, became ++++. There was no clinical evidence of any infection or other unrelated cause for this change. Although the prothrombin concentration returned to normal values within four days, the cephalin-flocculation reaction remained ++++ until the twenty-eighth day of the study. Five grams of methionine was administered by mouth, starting two days after the cephalin-flocculation reaction had become strongly positive, on the twentieth day of the study. On the ninth day of elevated cephalin-flocculation reaction, a high-protein diet was again given, since the patient felt extreme malaise and had diarrhea. Three days before the high-protein diet was re-instituted the cephalin-flocculation reaction was +++, and on the first day of the high-protein diet it became + and remained at that level. Methionine was continued. Subjectively the patient improved two or three days after institution of the high-protein diet. The final months of this patient's illness were complicated by dental sepsis, and the interpretation of results is therefore difficult.

Discussion

The importance of the liver in the pathogenesis of hepatolenticular degeneration has been discussed in a previous paper.[1] These considerations suggested a trial of dietary therapy in this disease. The state of health of such patients is hard to evaluate, since liver-function tests sometimes fail to reveal disease that is actually present. In these cases, the cephalin-flocculation test of Hanger was found to be the only liver-function test that gave results corresponding reasonably well with the clinical course. In 1 case[1] the cephalin-flocculation reaction indicated liver disease, whereas all other tests were negative and biopsy revealed extensive liver damage. False-positive reactions are extremely rare in this laboratory, where normal controls are run with each lot of antigen. In every case cephalin-flocculation reactions that indicated a change of liver function were repeated several times before they were considered significant. Thus, it appears reasonable in this disease to judge the hepatic status from the results of cephalin-flocculation tests. The changes of the tremor may be minor ones at best, since one would not expect regression of a symptom largely caused by irreversible neurologic damage. Continued observation over a long period of time is therefore necessary, and great co-operation by the patients is needed to elucidate the question.

During the period of observation covered by the present report, the initial impression of the usefulness of dietary measures in this disease was con-

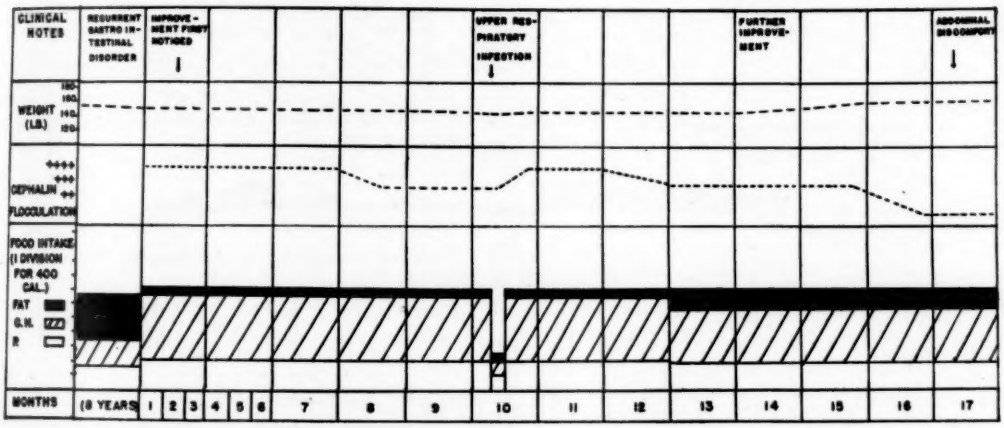

FIGURE 2. *The Course of Case 2.*

There was slowly progressive improvement of hepatic function on an adjusted diet. The relapse coincided with a lowered food intake and an upper respiratory infection. (CH = carbohydrate; P = protein.)

firmed. In Case 2, a clear-cut improvement was observed, unlike anything the patient had previously noticed. The cephalin-flocculation reaction, which had previously been persistently high, came close to normal and remained so for a considerable time. The patient experienced none of the formerly frequent gastrointestinal disturbances.

The course in Case 2 was complicated by recurrent minor infections. On the whole, however, the patient's condition improved. On the basis of György's[2] and Himsworth and Glynn's[3, 4] experimental work and because of recent favorable clinical nutritional components offered. In this case the caloric intake was not changed, but the substitution of protein and carbohydrates for the excessive amount of fat that the patient had been used to brought the observed changes in his condition. On the other hand, in the experiment done in Case 1, substitution of carbohydrate for most of the protein caused immediate failure of liver function and clinical distress, although the diet was kept isocaloric.

The final impression gained from this study is that high-protein diets are of definite value in im-

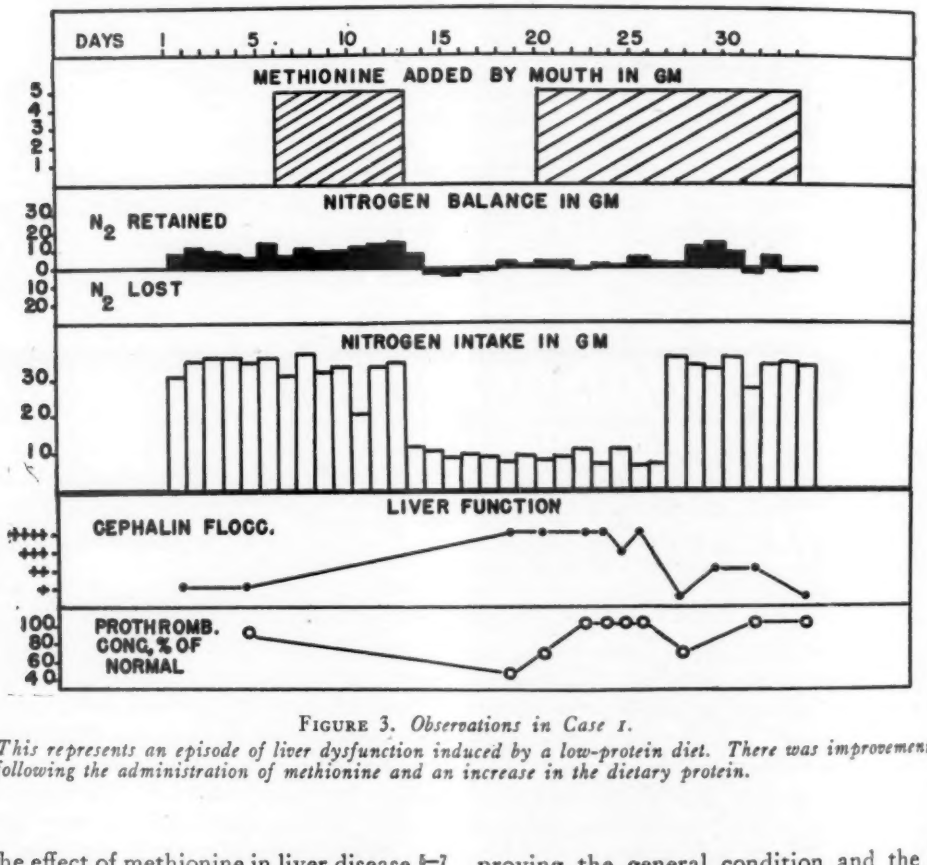

FIGURE 3. *Observations in Case 1.*
This represents an episode of liver dysfunction induced by a low-protein diet. There was improvement following the administration of methionine and an increase in the dietary protein.

reports on the effect of methionine in liver disease,[5–7] the effect of this amino acid on the liver dysfunction was studied. By a mere change in diet it was possible within a few days to produce serious hepatic impairment, with marked malaise and weakness. It appears that methionine alone added to the low-protein diet tended to correct this difficulty, although it was unfortunately necessary to reinstitute a high-protein diet before the effect of methionine alone could be properly evaluated. It seems clear that the addition of methionine to the high-protein diet over a period of more than a month added nothing to the beneficial effect of the diet.

The observations made in Case 2 suggest that it is not the total amount of food supplied that influences the course of the disease, but the type of proving the general condition and the liver function of patients with hepatolenticular degeneration. The addition of methionine to such diets as a long-term form of therapy is not useful. It seems possible, although it is by no means conclusively proved, that methionine has some beneficial effect when the protein content of the diet is too low.

The ease with which liver failure can be provoked in such patients by mere dietary restrictions may prove a useful tool in the further investigation of this disease. Continued study of such patients, preferably for periods exceeding their mean life expectancy, may bring a better understanding of the pathogenesis and possibly the discovery of therapeutic means of preventing the progression of the disorder.

Summary

Two patients with hepatolenticular degeneration were given high-calorie diets rich in carbohydrate and protein but poor in fat. Their clinical course and their liver function were followed. It appeared that with such diets there was clinical and functional improvement in both patients, whereas in the sister of one of the patients, who refused dietary measures, the disease progressed in the usual manner.

In 1 patient, lowering of the dietary protein with maintenance of the caloric value of the diet was followed by hepatic dysfunction. The favorable long-term effects of the high-protein diet were not enhanced by the addition of methionine.

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HEALTH BILLS PENDING IN CONGRESS*

Part Two

FRANZ GOLDMANN, M.D.†

NEW HAVEN, CONNECTICUT

ON November 19, 1945, President Truman sent a message to Congress requesting legislation for adoption of a national health program. In it, he stated: "We should resolve now that the health of this Nation is a national concern; that financial barriers in the way of attaining health should be removed; that the health of all its citizens deserves the help of all the Nation."

To meet present problems the President[1] recommended the adoption by Congress of "a comprehensive and modern health program for the Nation, consisting of five major parts, each of which contributes to all the others." The proposals deal with construction of hospitals and related facilities, expansion of public-health, maternal and child-health services, medical education and research, prepayment of medical costs and protection against loss of wages from sickness and disability. Immediately following the reading of this message, the new Wagner–Murray–Dingell Bill (S. 1606 and H.R. 4730) was introduced.

The National Health Bill

Summary of Provisions

The general intention of the National Health Act of 1945, sponsored by Senators Murray and Wagner and Representative Dingell, is to provide for a national health program. The bill is arranged in two parts. Title I deals with the extension and improvement of already existing health services. Title II proposes the introduction of prepaid personal health service benefits.

Title I makes provision for the generalization of programs for the prevention, treatment and control of venereal diseases and tuberculosis, of general public-health work and of maternal and child-health services, including programs for crippled children, and for a unified system of medical care for needy persons. Pertinent details are described in a Senate Committee report[2] as follows:

> State plans to be approved must provide that programs be in effect in all political subdivisions (1) by 1949 for public health programs; (2) within ten years after date of approval of first State plan for maternal and child-health service, and (3) immediately, for plans for medical care of needy persons.
>
> (1) State plans for public health must provide for extension and improvement of public health work toward achieving nationally accepted standards; (2) State plans for maternal and child-health services must provide that the services and facilities furnished shall be available to all mothers and children in the State or locality; (3) State plans for medical care of needy persons must assure meeting in full the need of individuals for medical care throughout the State . . . and may not impose citizenship or residence requirements. . . .

To finance the expansion of these services the federal government is to pay not less than 50 per cent and not more than 75 per cent of the state expenditures made for the various programs mentioned. The allocation of funds is based on a so-called "variable-matching" basis, so as to give the poorer states special aid.

The present division of administrative authority remains unchanged. At the federal level the public-health program is to be administered by the United States Public Health Service, the maternal and child-health program by the United States Children's Bureau and the program of medical care for the needy by the Social Security Board. As in the past,

*This is the second of a series of four lectures on medical sociology given at the Harvard Medical School during February and March, 1946. They were sponsored by the Department of Preventive Medicine and were primarily intended for third-year students.

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the administration of direct service is to be left to the states and their political subdivisions.

Title II deals with the controversial problem of health insurance. This program covers every currently insured person and applies to all employees in industry and commerce (except railroad workers), agricultural and domestic workers, employees of nonprofit institutions and all self-employed persons, such as independent farmers, small-business men and professional persons. In addition, the family dependents of all those insured are to be automatically eligible for service, and the recipients of retirement or survivor's benefits under the Social Security Act are included. The basic principles, therefore, are broad coverage, effected by including the large majority of the American people, and service to the family rather than to the breadwinner only.

The scope of the service proposed is fairly comprehensive, and its extension would be possible under certain conditions. There are included the services of physicians and dentists, specialists as well as general practitioners, home nursing, laboratory services and hospitalization up to sixty days in any benefit year. Hospital care may be extended up to one hundred and twenty days if sufficient funds are available.

The organization of professional services is based on the utilization of the system of private practice of medicine, dentistry and allied professions and the application of the free-choice principle. As the bill clearly states, "Any physician, dentist or nurse legally qualified by a State to furnish any services included as personal health service benefits . . . shall be qualified to furnish such services." The physicians and the members of the related professions are free to join the program, if they so desire. As it should be under a system guaranteeing freedom of choice, "any group of physicians, dentists or nurses, or combinations thereof" are to be admitted to the service, and thus a firm legal basis is created for the development of group practice of medicine. The patients, too, have free choice, although with limitations. The bill states, "Every individual entitled to receive general medical or general dental benefit shall be permitted to select . . . those from whom he shall receive such benefit . . . and to change such selection." Wisely, the bill proposes that "the services of a specialist or consultant shall ordinarily be available only upon the advice of the general or family practitioner or of a specialist or consultant attending the individual." If enacted, the bill will serve to give the general practitioner or the family physician a key position in the program and to prevent the indiscriminate use of specialists.

As regards the method of paying for the services of general practitioners, the bill permits the fee-for-service system, the per capita basis, — that is, a flat rate for each person on the list of the practitioner, — salary compensation and a combination or modification of these methods. The decision rest with the general practitioners in a given a and the majority vote is to be binding. The muneration of specialists is based on function, the paying of special rates to "those qualified furnish . . . specialist or consultant services."

Hospitalization is to be provided by all hospi willing to participate in the program, the criterion of admission being their standards of p fessional service, personnel and equipment. Th voluntary as well as governmental hospitals will utilized.

To finance the service the bill proposes to emp the method of prepayment, but does not specify rate. From sentences in the bill and statements the President and others it may be assumed th the rate will approximate the average proportion the income actually spent on medical care by persons and families. As the President pointed o in his recent annual message to Congress, "The sy tem of prepaid medical care which I have reco mended is expected eventually to require amoun equivalent to 4 per cent of earnings up to $3600 year."

The administrative organization of the service based on two principles. Public agencies, rath than nongovernmental organizations, are to vested with administrative authority, and decen tralization of administration of direct service is em phasized by dividing powers and functions betwee federal agencies on the one hand and state and loc agencies on the other. At the federal level, the re sponsibility for the program rests with the Surgeo General of the United States Public Health Servic who is to act under the supervision and direction o the Federal Security Administrator and after con sultation with the newly established National Ad visory Medical Policy Council. This council is t advise the Surgeon General with reference to que tions of general policy and administration and i to consist of the Surgeon General, as chairman and sixteen members to be appointed by him. Th membership of the council includes medical an other professional representatives and public repre sentatives. The guiding principle is to provide fo broad representation of all groups concerned, s that the Surgeon General and his staff can have th benefit of the advice of all who have something t contribute. At the state and local levels, the facilitie and services of state and local departments o agencies will be utilized preferably, and here als advisory committees, called "local-area committees, are to be established.

Discussion of Provisions

Any plan for the improvement and extension o health services must be judged strictly on the basis of merit. Unbiased analysis of the National Health Bill shows strong and weak points.

The provisions of Title I can be expected to exert powerful and beneficial influence for the badly eded further extension and improvement of neral public-health, maternal and child-health rvices. At long last the sound development of iform medical-care programs for the needy will be tiated. But there are weaknesses that should be minated. As it stands, the bill evades the unniably intricate problem of unification of the dministration of health services at the state levels, us continuing the policy of vesting authority in multitude of state agencies. To give an example, enty-two of the crippled-children programs are lministered by agencies other than health departents. The measure requires the establishment of single public-assistance agency to administer or supervise the state's medical-care program for e needy. Thereby it would bring about a conderable improvement but would also perpetuate e old evil of dual administration, the publicssistance agencies being responsible for the medical re of the needy and the health agencies having uthority for the medical care of self-supporting ersons as well as preventive health services for ll. At the federal level not less than three agencies re charged with administrative responsibility, and o-operation and correlation, typical *Ersatz* prodcts, are recommended. The sections dealing with edical care of the needy fail to eliminate the utterly inadequate method of making cash allowances or the payment of bills and do not require the use f the prepayment method for the support of servces to the needy.

Title II invites many comments on both strong nd weak points. The right to medical care is estabished for all those covered by the program, wherever hey live and whatever their income. With this here is being approached the realization of an old American dream — that of the equality of opportunity for everybody to obtain adequate medical care. Fairly complete service is organized for the majority of the people under one program, in contrast to the old policy of offering more or less limited service to selected socioeconomic groups under different programs. Broad coverage is essential from an actuarial point of view, since it makes for effective and economical operation of a plan in which risks and resources are pooled. The scope of the service, fairly comprehensive as it is, compares favorably with that of many voluntary health-insurance plans in operation. Continuation of the system of private practice of medicine, dentistry and related professions and freedom of choice, as proposed in the bill, are the very principles for which the professions have been fighting ever since organized care of the sick has existed. Thus, the professions are offered a unique opportunity to make the program work. The system of voluntary hospitals is maintained in conformity with the concepts and wishes of those who want scope and a chance for voluntary effort and philanthropy. Preventive medicine is encouraged through the combination of an organized program for the care of the sick with a system of services for the prevention of illness and the promotion of good health; the inclusion of diagnostic laboratory services; the inclusion of preventive services and of periodic physical examinations — or periodic examinations in the case of dental service; and easy access to early treatment. The quality of medical care is promoted by the comprehensiveness of the program; the exclusion from the service of persons other than legally qualified physicians, dentists and nurses; the encouragement of group practice; the availability of consultant and specialist services; the many provisions for the maintenance of professional and hospital standards; and the provision of funds for research and professional education. The proposed method of raising funds for the support of the program is sound and has a long and honorable record in this country as well as a score of foreign countries. It is superior to other methods of finance, because it substitutes organized self-help for charity from the few to the many, eliminates application for aid and determination of eligibility on the basis of financial need and relieves the administration of the cumbersome procedures inherent in any system utilizing the so-called "means test."

On the debit side of the ledger quite a few items have to be entered that deserve careful consideration. The success or failure of any health program, no matter how it is financed, depends on the willing and understanding co-operation of the members of the various health professions: in other words, doctors can make or break it. The Wagner–Murray–Dingell Bill gives the members of the professional groups important rights and defines them in detail, but it contains nothing about the duties of the professions, except for the statement that the general practitioners in the local areas who are participating in the program have a collective responsibility to provide the general services. The question is therefore warranted whether a satisfactory operation of the program can be expected if the individual physicians have freedom of participation and the medical profession has no collective responsibility for the availability of professional services. As asserted by Becker,[3] "This is indeed the central problem of all political philosophy and practice, the problem of the one and the many — the difficulty being to reconcile the desirable liberties of the individual with the necessary power of government in such a way as to do justice as well as may be to the desires and the interests of all individuals and classes in society."*

In this connection attention must be called to the difficulties that are certain to arise from the lack of nation-wide licensure. The diversity of state laws is anything but conducive to the better distribution of physicians.

*Quoted by special permission.

The statements covering the proposed administrative organization need amplification and reformulation. In rewriting the pertinent sections each of the following points should be treated under separate headings and elaborated on: distribution of administrative powers, duties and functions among the various levels of government, including the creation of effective local units of administration; professional direction of the service at the federal, state and local levels; participation of the health professions, hospitals and various health and welfare agencies in the organization and administration of the service; and the relation of the prepaid personal health services to other medical-care programs and health services under public and voluntary auspices. Emphasis should be placed on utilizing the prepayment service for all rather than operating one program for the majority of the self-supporting people, another for recipients of public assistance and still another for veterans. The unique opportunity to unify the administration of all health services must not be missed. Preventive health services and medical-care programs should be under a single agency. For reasons of expediency the bill omits any proposal that would bring order out of administrative chaos and is content with the makeshift arrangement of co-ordination. But even this idea is not followed through, since little is said about co-ordination at the state and local levels.

Another weak point is the exclusion of drugs. The difficulties involved in the effective and economical organization of supply with drugs are indeed great. As it stands, the bill raises knotty problems. Many physicians—and not only those in rural areas—dispense their own drugs in attending patients. Are they to receive payment for an office visit made by the patient only for the purpose of having his prescription refilled? Are the drugs furnished as part of the hospital care to be included in the "reasonable cost of hospital service"? Would exclusion of drugs from the contract induce the hospital to make substantial extra charges for this service?

The proposed rates of payment for hospitalization do not cover the actual cost of care in the best hospitals and thus penalize institutions maintaining the highest standards.

The fee-for-service system of payment, one of the various methods offered for selection, has implications that seem to be overlooked by many physicians. As ample experience has shown, combination of the free-choice panel system with the fee-for-service method of payment makes it obligatory to employ cumbersome, annoying and costly devices for the control of expenditures. This lesson has been learned by many medical societies co-operating with public agencies in the administration of programs of public medical care or sponsoring voluntary health-insurance plans. To hope for a sa factory operation of the program without such c trols is to display a naïve faith.

Important as the shortcomings of Title II a they are outweighed by its advantages. In b titles of the bill, phraseology and arrangement le much room for improvement. Even experts w have to spend countless hours on the analysis the bill — and may still miss a point. It will doubly difficult for the general reader, not to m tion the busy physician, to avoid misinterpretati and erroneous conclusions. A bill dealing w questions reaching to the heart of the anxieties everyone should be logically and clearly organiz and written in a language fully understandable the common man.

Relation to a Broad National Health Program

According to its title, the bill is to provide for national health program. Actually, it deals wi two essential parts of it — namely, public-heal services and organized care of the sick. Missi from the bill are proposals for the construction hospitals and related facilities, the protection of t sick against economic losses caused by disabling il ness and the care of patients with protracted il nesses.

The first problem is taken up in the Hill-Burto Bill, to be cited as the Hospital Survey and Co struction Act. Disability insurance is to be include in the revision of the Social Security Act. Th problem of services and facilities for the care of th chronic sick afflicted with physical ailments an of persons afflicted with mental or nervous disease is to be studied by the Surgeon General of the Unite States Public Health Service, and is to be reporte on with recommendations for legislation not late than three years after the effective date of Title I of the Wagner–Murray–Dingell Bill.

All the bills mentioned are interdependent Adoption of Title I of the Wagner–Murray–Dinge Bill and rejection of Title II, adoption of the whol bill without passage of complementary bills, such as the Hospital Construction Bill, or enactment o the Hill–Burton Bill without provision for organize payment for services would seriously hamper th development of an effective and economical nationa health program. No country alert to its social ob ligations in the field of health service can afford thi luxury of piecemeal procedure and half-measures.

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CARDIAC ARREST AFTER SPINAL ANESTHESIA

Report of a Case with Recovery

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THE occurrence of cardiac arrest under anesthesia is fortunately extremely rare. The apparent reason is that the respiratory center is much more sensitive to anesthetic agents than is the cardiac center, so that fair warning is given of impending disaster by cessation of respiration before the heart stops.

In reviewing the literature one finds a considerable number of deaths reported after spinal anesthesia. These are of two types, the immediate and the delayed. The former occur before or shortly after surgery commences. The latter may occur several hours after the patient leaves the amphitheater. This report concerns a case with collapse of the immediate type.

Veal and Van Werden[1] report 30 immediate deaths in a series of 33,811 cases given spinal anesthesia. This and other reports emanate mostly from the large medical centers, and one wonders whether there may not have been many similar but unreported accidents in the smaller hospitals. The cases in the literature are often too sketchily reported for one to know whether the heart or the respirations ceased first. "The patient died suddenly" is the usual statement in such reports.

Graham and Brown[2] report 5 fatal cases, in 2 of which death occurred just after the abdomen had been opened. These 2 cases were comparable to the one reported herein.

MacLeod and Schnipelsky[3] describe a case with successful outcome in which cardiac massage was combined with the intracardiac administration of adrenalin. The heart ceased beating for three and a half minutes, and artificial respiration was kept up for forty-five minutes. The patient recovered after a forty-eight-hour period of cerebral edema. These authors stress the necessity of teamwork in performing cardiac massage and artificial respiration and clearing the airways.

Adams and Hand[4] report a remarkable case of cardiac arrest for twenty minutes with complete recovery. The patient was undergoing a pulmonary operation when the heart ceased beating. It was sustained by cardiac massage and artificial respiration during the period of cessation. The authors emphasize the necessity for these two measures in preventing death.

CASE REPORT

A 62-year-old woman was admitted to the Portsmouth Hospital on June 15, 1945, for cholecystectomy. On a previous admission on February 15, 1943, she had been examined for a continuous dull ache in the right flank, which had been present intermittently over a 10-year period. The pain seemed to be renal in location and was distributed along the course of the right ureter. An intravenous pyelogram revealed a small shadow on the right, which appeared to be a congenital atresia of the kidney. Cystoscopic examination failed to show any ureteral orifice on the right side. This presented two possibilities. An extremely small opening might connect a congenital kidney with the bladder, or there might be no opening, a small kidney with some secreting elements causing pressure and pain. Thorough exploration carried out in the region of the right kidney gave no sign of a renal or embryonic abnormality. An explanation of the shadow appearing on the x-ray plates was difficult. It may be that the gallbladder concentrated the dye. In the course of the operation the peritoneal cavity was accidentally opened, and by means of a palpating finger the gall bladder was felt to contain stones. The wound was closed with drainage, and the patient had an uneventful convalescence. From that time until the 1945 admission, there was recurrent biliary colic. There was no history of jaundice, biliuria or clay-colored stools. The most recent attack of severe biliary colic and vomiting had occurred 2 weeks before entry. There had been no weight loss.

Physical examination was negative except for a blood pressure of 180/90. Urine examination was negative, and the red-cell and white-cell counts and hemoglobin level were within normal limits. The icteric index was normal.

On June 16, a spinal anesthetic was given. Premedication consisted of 0.2 gm. of pentobarbital sodium at bedtime, 0.2 gm. of pentobarbital sodium 1 hour before surgery and 10 mg. of morphine sulfate 30 minutes before surgery. Eighteen milligrams of pontocaine in 3 cubic centimeters of 10 per cent glucose was placed in the subarachnoid space through the 3rd lumbar interspace. The patient was put in the moderate Trendelenburg position, and in 2 minutes the table was straightened out. The operation was begun 11 minutes after the anesthetic agent had been administered. Two minutes later, intravenous administration of 10 per cent glucose was begun because of a drop in the blood pressure. Exact timing during a crisis in the operating room is difficult to obtain, but determinations of the periods of cardiac and respiratory arrest were accurate within 30 seconds.

The patient stopped breathing 43 minutes after the operation was begun, but there was ample time to make a splitting incision of the right upper rectus and enter the abdomen before this occurred. Since the artificial-respiration machine was not immediately available, manual artificial respiration was begun and was carried out for a minute or so before an attempt was made to feel the heart beat through the diaphragm. No impulse could be detected. Cardiac massage was immediately instituted. The heart was compressed firmly against the chest wall, and there was a faint flicker of response. The heart was massaged firmly for 1 minute, and artificial respiration was then applied for a few respirations, with the oxygen mask on the face. During the next 5 minutes cardiac massage was alternated with artificial respiration. The heart flickered a little more firmly with each compression, and it had re-established a slow firm beat at the end of 5 minutes from the time that cardiac arrest was first noted. This return to a full, normal beat was quite sudden. Just before this, there had been only a slightly stronger flicker in response to massage, but the heart suddenly leaped from the hand and maintained a firm, regular beat. The blood pressure immediately rose from 0 to 170/90.

Artificial respiration was carried out by hand for 30 minutes after the onset of respiratory arrest. An Emerson resuscitator was then applied and artificial respiration was continued for another 5 minutes, when spontaneous respiration occurred. The gall bladder was removed, the abdomen was closed in layers, and the patient was returned to her room

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in good condition. The blood pressure and pulse showed no deviation from normal at that time.

The patient's general response for 24 hours was that of a decerebrate. She could move her arms and legs, and there was no evidence of paralysis. The pupils were equal and of moderate size and reacted to light. At 3 p.m. the patient had extremely quiet respirations and seemed to be slipping into deeper and deeper coma. One cubic centimeter of Coramine was given intravenously, and this drug was given at hourly intervals for the next 24 hours. At 9 p.m. 2 cubic centimeters of metrazol was given subcutaneously, and this dose was repeated every hour during the night, but was discontinued 24 hours after the operation.

The day after the operation the patient showed signs of restlessness, moving both the arms and the legs. She swallowed water when so directed and also opened her eyes when asked a question. By the following day she had gradually become conscious, spoke and recognized people and moved all her extremities. There was some nausea but no vomiting. She had no recollection of recent events and did not recall the operation or coming to the hospital. On the next day she was fully conscious, ate well, voided and took fluids, and so far as could be determined there were no residual neurologic signs. The knee jerks were equal and normal. The pupils reacted well and there was no evidence of any muscular weakness. Six days after the operation the patient had frequency, dysuria, chills and fever. She was placed on sulfadiazine and improved greatly during the next 2 days. Twelve days after operation she was able to go home, still showing no signs of neurologic disturbance. The wound had healed by first intention. Since then she has been seen on several occasions, and 4 months after the operation was quite well.

Discussion

The mechanism of death from spinal anesthesia has been investigated experimentally by Seevers and Waters.[5] Their summary deserves full quotation.

> Our conception of the train of events occurring during untreated high spinal block is as follows: initial decrease in peripheral resistance to blood flow by vasomotor nerve and skeletal muscle paralysis; decrease in minute volume respiration accompanying intercostal nerve paralysis; inadequate oxygenation of blood; diminished minute volume of blood flow; progressive loss of vascular tone over the whole body and acute cardiac incompetence, both the result of oxygen deprivation; failure of the medullary respiratory mechanism as the nutrient flow of blood becomes inadequate, the latter occurring while the heart is still capable of being revived by oxygenation.

The obvious treatment is arrest of these developments at the earliest recognized stage. The use of vasoconstricting agents, infusions, oxygen and stimulants is too well known to require discussion. The case reported represents the rare catastrophes in which all the above stages are passed through so rapidly that at one moment one is confronted with a fairly normal patient and at the next is faced with a dying patient. Beecher[6] has suggested that this sudden collapse may be due to sensitivity of certain patients to the drug rather than the effect of an overdose. This seems a reasonable assumption in view of the marked differences in the reactions of different subjects to the same agent.

It is interesting that the 2 other similar cases in the literature[3, 4] were treated by cardiac massage and artificial respiration. On the basis of these three successes one cannot be dogmatic, but one can suggest that the following line of treatment be tried. When a patient under spinal anesthesia stops breathing, artificial respiration with oxygen should be begun, and it should be ascertained whether the heart is beating. The latter is easy when the abdomen or chest has been opened. If no incision has been made and a reasonable doubt exists concerning cardiac arrest, either the abdomen or the chest should be opened at once. To one who has given cardiac massage it seems impossible that this procedure can be performed except through the abdomen or chest.

By cardiac massage and artificial respiration with pure oxygen, even over a considerable period one can in most cases revive the heart and save the patient.

The use of stimulants (Coramine and metrazol) during the postoperative period seemed of great value in this case. Adams and Hand caution against the administration of cardiants except in physiologic doses during the period of cardiac arrest.

Summary

A case of cardiac arrest under spinal anesthesia is reported. Whenever respiration ceases under spinal anesthesia one should be certain that the heart is functioning. If the heart is not beating and the abdomen has not been opened, a laparotomy should be done immediately and cardiac massage instituted. This procedure, if undertaken early enough, may save life by returning the heart to its normal function.

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MEDICAL PROGRESS

NORMAL GROWTH AND DEVELOPMENT DURING ADOLESCENCE*

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SKELETAL OR OSSEOUS DEVELOPMENT

The characteristic picture of the development of the skeleton as seen in roentgenograms of the hand and other areas has been studied in great numbers of children at each age, and standards representing average occurrences have been published. The *Atlas of the Hand* prepared by Todd[26] is the most extensive of these and serves as a practical standard for comparing subjects. Flory[27] has prepared an additional set of standards, and a number of other methods have been suggested. Space does not permit a review of the changes taking place year by year throughout adolescence, but the characteristic patterns of development in the hand at the beginning and at the end of pubescence are sufficiently important to justify their description.

Flory states that the average x-ray picture of the hand and wrist of a girl at eleven years shows the carpal area to be so full that the shadows may overlap in several directions. Practically all the bones have their adult shapes, but the pisiform is usually quite small. A sesamoid should normally be present at the distal end of the first metacarpal. The gaps between the epiphyses and diaphyses are for the most part quite small, but no union has taken place. The radial hook or beak is quite pronounced, although there is still a roundness on the outer side.

At thirteen years in girls, according to Flory, the metacarpal heads have started to fuse but the phalangeal epiphyses are still open. There is definite parallelism between radial and ulnar epiphyses and their shafts, and all the epiphyses are in readiness for fusion. The carpal area seems filled to adult capacity, and the naviculare has come into a functional relation with the radial epiphysis.

Full union of all epiphyses in the hand and wrist does not take place in girls until seventeen years, although by fifteen years all but the radial and ulnar epiphyses are nearly united and the latter shows beginning union.

Most writers have found that the comparable stage of osseous development is attained during adolescence on the average between one and two years later in boys than in girls. According to the table of age equivalents presented by Todd,[26] based on x-ray films of the hand, the average girl of nine years is about one year advanced in osseous age over the average boy of that age, and at eleven she is about eighteen months advanced. After twelve years of age she is two years ahead until she has reached osseous maturity in this area. This indicates that, in association with other pubescent changes, osseous maturation is accelerated. The girl is one year ahead of the boy in this respect during the prepubescent period, but owing to the acceleration of pubescence that occurs with her two years before it does with the boy, she becomes one year further advanced. As a matter of fact, the description of the hand of the average girl at eleven years as given by Flory applies almost equally well to the boy of thirteen years, and that for the girl of thirteen years may be taken as characteristic of the boy of fifteen.

Some children are quite irregular in osseous development, and the impression gained from the study of one aspect of the hand or one part of the body may be quite different from that obtained from another. In these cases it is difficult to assign an exact osseous age. With experience, however, it is usually easy to recognize from x-ray films of the hand the children who are either advanced or retarded in osseous age for their chronological age. Variability in this respect is quite as great as that in other aspects of development. The interrelations between advancement or retardation in osseous development and other aspects of growth and maturation will be considered in a later section of this report.

PRIMARY AND SECONDARY SEXUAL CHARACTERISTICS

There is a natural sequence in the manifestations of development of the sex characters, just as one has been shown to exist in the patterns of growth and ossification. This sequence is followed with great consistency, but there are marked differences in the chronological ages at which different milestones are passed, both between the sexes and among members of the same sex. There are also considerable differences in the degree of differentiation or in the magnitude of change in size to which any attribute attains. Hence, there is a wide range of variability in the size or general appearance of the sex characters and the functional state of the sex organs of boys or girls of the same chronological age, particularly between ten and eighteen years of age.

Development of Male Sex Characters

Schonfeld[28] classifies the testes, the epididymes, the seminal vesicles, the prostate, the genital passages and the penis as primary sexual organs. These are rudimentary structures in infancy and remain so, although growing slowly, until the onset of pubescence. All the secondary sex characters — that is,

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the pubic, axillary and facial hair and the male quality of voice — make their first appearance at different intervals after the rapid growth of the primary characters has begun, and they reach different stages but usually not complete development during pubescence. Associated with the maturation of these secondary characters and properly considered among them is rapid growth of muscles and bones in certain groups or parts that leads to masculine contours and proportions. These changes also continue well into postpubescence.

According to Schonfeld, the epididymis is relatively large in comparison with the testis before the onset of pubescence, being one third to one quarter the size of that organ. During pubescence and postpubescence the testes grow much more rapidly than the epididymes, so that in the adult the latter are only one ninth the size of the former. The accelerating growth of the testes begins at about eleven years of age but does not become rapid until about fourteen years. It has reached its peak by seventeen years, after which deceleration takes place. Thus, rapid growth of the testes begins at about the time of maximum linear growth and continues until it has ceased. Under eleven years of age the length of the testis is usually between 1.5 and 2.0 cm. and its weight is about 2 gm. By eighteen years of age its length is usually between 3.5 and 5.0 cm. and its weight is about 17 gm.

The penis approximately doubles in both length and girth in association with the enlargement of the testes. The prostate, which is hardly palpable before pubescence, increases rapidly in size and changes markedly in shape and contour during this period. Evidence of prostatic secretion appears fairly soon after the gland begins to enlarge, or between ten and eleven years, but active spermatozoa are not found until considerably later. Motile mature spermatozoa are not usually found until fifteen or sixteen years, although Baldwin[29] has reported them in morning urine specimens of boys in increasing percentages after thirteen years. These functional activities are, of course, dependent on differentiation within the structure of these organs. Growth in size is only an indication that this differentiation is under way, but the histologic changes that accompany this growth cannot be considered in this review.

The goal of all changes in the primary sex characters is the capacity to reproduce, and the age at which this capacity is fully developed is by definition the end of adolescence. The appearance of morphologically fully differentiated motile spermatozoa in the semen is usually accepted as evidence of the capacity to reproduce, but this is not necessarily an indication that full sexual maturity has been attained. The evidence concerning the time when this stage is reached in boys is far from adequate, but by inference from that for comparable development in girls, which is considered below, it is after general growth has begun to slow down, if it has not fully ceased, after most of the epiphyses of t long bones have fused with their diaphyses, aft all the secondary sex characters are well advanc and probably some time after spermatozoa ha appeared.

The range of variability in the time of occurren of these developmental stages of sexual maturati may be judged from Schonfeld's study of the grow of the testes. He found that in 80 per cent of t boys in his group, the age of onset of rapid testicul growth was between twelve and sixteen years, a that the range for the termination of this rap growth was sixteen to twenty years. Thus, exclu ing the extremely advanced and the extremely r tarded boys, there was still four years' difference the time of occurrence of these changes.

Greulich and his collaborators[30] made a most d tailed study of the successive stages of the develop ment of the principal male secondary sex character that of adult body hair. All the stages recognize by these writers will not be listed here, because ob servation of all the parts involved does not seem necessary for clinical purposes. The character an distribution of hair in four locations should, how ever, be noted in the routine examination of adole cent boys, since the successive stages of development of the hair are closely correlated with less easil recognized but more important sexual attribute The four characteristic locations for the appearanc of maturing hair, in the order of their appearance are the pubic region, the axillas, the face and cer tain areas of the trunk and extremities. The develop ment of dense, coarse, deeply pigmented, long an in some locations curly hair, which is the characteri tic of maturity in these parts, follows a series o transitional stages from the fine, short unpigmente vellus hair of childhood. Hence, the character an density of the hair are worth noting, as well as th locations within which it has appeared.

In almost all cases the pubic region is the first i which maturing hair is seen, and the developmenta changes in its characteristics in this region are spread over a major portion of the period of rapid develop ment of the other sex characters. Hence, the ter "pubescence," which derives from this sex character may properly be used to signify this central an major period of adolescence. The first change to b noted in the pubic region occurs shortly after th accelerating growth of the testes and penis has begu and consists of a denser, longer vellus hair about th base of the penis. Shortly thereafter occasiona longer, coarser pigmented straight hairs appear Still later these become dense, and finally they begi to curl or kink. As these changes are progressing the area involved spreads out laterally to the in guinal creases and gradually upward to the pubi crest. At this stage, which usually coincides wit beginning deceleration of growth, fairly dense, long pigmented hair fills this area, forming the inverte triangle characteristic of adult female distribution

Thereafter, and usually during postpubescence, pubic hair extends further upward toward the umbilicus and outward to the femoral areas of the thighs. With these latter extensions the diamond-shaped distribution characteristic of the adult male is attained and the central hair becomes even more dense and kinked, but the amount or extent of these advanced stages attained varies greatly. After pubic hair has been present for some months, but while it is still localized about the base of the penis, mature hair begins to appear in the axillas, first as sparse, long pigmented hairs centrally located but progressing in area, type and density, as in the pubic region.

Facial hair first appears after considerable axillary hair is present, and it progresses in a characteristic manner. It begins laterally on the upper lip, spreading medially, and appears in succession over the upper part of the cheeks, centrally under the lower lip, on the chin and under the maxillas, finally spreading down to the neck and up to the face. Again the progression is from sparse to dense and longer vellus hair appearing like down, then as occasional longer, darker and thicker hairs and finally as dense, coarse adult hairs. At this time in boys the hair line on the forehead may begin to recede on either side, producing the laterally indented configuration of the masculine type, but this change may begin much later and progress gradually into adult life. During these stages longer, coarser pigmented hairs are often developing amid the vellus hair on certain parts of the extremities and about the nipples, but the extensive development of mature hair on the chest and on the extremities comes later and continues well into adult life. The degree of this development varies greatly.

Development of the breasts of boys is variable and only rarely marked, but some changes are seen quite regularly. The usual one is an elevation of the nipples on a slightly full areola. Occasionally a mass of firm, sharply demarcated tissue several centimeters in diameter underlies this areola and gives the appearance of true breast development. This occurs at about the time dense, dark pubic hair is present at the base of the penis and when axillary hair is beginning to appear. This tissue disappears after a variable number of months, depending on its degree of development.

Change of voice is a late manifestation of the pubescent period in boys, but the larynx develops rapidly throughout pubescence, increasing in internal dimensions, with associated changes in the vocal cords. The voice, however, usually does not begin to acquire the deeper tone characteristic of the mature male until the fifteenth year.

Each of the phenomena described passes through several developmental phases covering a considerable period of time, although varying among individuals. Since each phenomenon is initiated at a different time, an early phase of one quite regularly accompanies a later phase of another, and at any one time a characteristic combination of phases is to be expected. Collectively they span the period referred to as pubescence, and some continue to mature throughout postpubescence. The duration of pubescence varies to a certain extent but is rarely less than two years and may be considerably longer. As with growth, so with these manifestations of differentiation, those who begin to mature early tend to pass through this period rapidly, whereas those who mature late tend to progress through it more leisurely. Schonfeld[28] and Greulich et al.[30] have both attempted to classify boys into various precisely definable stages of pubescence. For clinical purposes, evidence that a boy has entered this period,—consisting of enlargement of the external genitals and the appearance of downy pubic hair, — that he has ended it — consisting of a deep voice, extensive facial and axillary hair and quite mature pubic hair up to the pubic crest — or that he is in a mid-stage of these changes seems to be sufficient. The association of these readily observable phenomena with the rapid phase of adolescent growth, with definite stages of osseous development, with rapid increases in the urinary excretion of the 17-ketosteroids and with certain immature functional activities of the sex organs, is the feature that gives them significance. This association will be considered more fully in a later section.

Development of Female Sex Characters

The evidence relating to the growth of the ovaries is extremely meager. It has been reviewed by Greulich and his associates.[5] As in the case of the testes, this is apparently very slow during the prepubescent period and is most rapid during postpubescence. Scammon[31] has shown by means of a graph that the characteristic features of the growth of the ovary are extremely slight progress up to eight years of age, moderately rapid and accelerating growth between eight and seventeen years and extremely rapid enlargement between seventeen and twenty years. According to this graph, the ovary at the time of the menarche has attained only 30 per cent of its ultimate weight. Apparently both the testes and the ovaries follow this pattern of maximum growth after development in most other respects has been substantially completed. If these data are correct, full growth of these organs is not essential for reproductive function. The growth of the uterus, according to Scammon, is that of a straight-line increase from about ten to eighteen years of age, during which time it approximately doubles in length. The uterus also changes considerably in shape and in the proportions of its parts during this period.

The first of the female secondary sex characters to appear is often the rounding out of the hips, but if this attribute is not to be highly developed, the first stage of breast development can be observed earlier.

This rounding out of the hips is due in part to broadening of the bony pelvis but more particularly to increased deposition of fat in the subcutaneous tissue of this area. Greulich and Thomas[32] have studied by means of repeated roentgenograms the developmental changes taking place in the pelves of adolescent girls. They have shown that during the prepubescent period the pelvis grows slowly and symmetrically. During pubescence, however, it not only grows much more rapidly but changes in shape and undergoes considerable remodeling. During this time the pelvis increases more rapidly in width than in depth, particularly in the plane of the superior pelvic aperture, and the fore part becomes widened and more rounded. This period of rapid growth and fundamental changes in the character of the pelvis usually requires about eighteen months for its accomplishment. The changes described ordinarily begin after the first signs of breast development have appeared, are well along at the time of the menarche and end shortly thereafter. During the postpubescent period there is apparently a slight further growth of the pelvis but not much further change in its shape.

The earliest changes in the appearance of the breasts are usually noticeable before any pubic hair is seen. In the prepubescent period the papilla is small and slightly elevated and the areola is flat. The first stage of pubescent development is characterized by elevation of the surrounding areola, causing embedding of the papilla in a small conical protuberance on a flat chest. This stage, known as the "bud" stage, generally develops in the eleventh year but not infrequently does so in the tenth to twelfth years. The second stage is primarily brought about by an infiltration of fat under and surrounding the areola, referred to as the "primary breast," which causes a further elevation of the areola and further embedding of the nipple. The third stage involves further enlargement of the breast itself with incorporation of the formerly elevated areola, so that only the nipple remains elevated. This is the so-called "secondary" or "mature" breast, but its size at maturity varies widely. The breast is most frequently in the primary stage at the time of the first menstrual period, but it may still be in the bud stage and occasionally has attained the form of the mature breast.

The vaginal changes that occur during the pubescent period have been observed by Pilcher and Tuchewicz.[33] The tissues about the hymen become hypertrophic, succulent and grayish, and the predominant organisms found on smears change from cocci to bacilli. The vaginal reaction changes from a prepubescent aklalinity of about pH 7.5 to a postpubescent one of about 4.5. The epithelial cells found in smears become cornified and contain glycogen. The exact stage at which these changes occur has not been determined, but it is thought that they usually come about at some time after the first stage of breast development, but several months, if not a year or more, before the first menstrual period.

The development of body hair is less extensive in the female than in the male, but its appearance and development in two locations is sufficiently characteristic and closely correlated with less obvious pubescent changes to justify attention. As in the male, the pubic hair appears first and the axillary hair appears after a considerable interval. The former begins above or about the labia and spreads medially and upward to the crest of the pubis and then laterally to the inguinal region. Characteristically it does not progress above the pubis, as in the male, so that the feminine form at maturity is that of a triangle, with its base above at the crest of the pubis and its apex below at the lower angle of the vagina. The axillary hair appears some time after the pubic hair and develops later, in much the same fashion as in the male. Pryor,[34] who classifies hair on the basis of amount and maturity rather than on the extent of area involved, gives four stages of pubic-hair development — unpigmented down, usually appearing between ten and a half and twelve and a half years; a few short pigmented semiterminal hairs, appearing six months later; terminal hairs of full length and pigmentation, wiry but sparse, appearing in another six months; and dense, fully mature terminal hairs, appearing between twelve and fourteen years of age. The comparable stages of axillary hair occur about six months later than those of pubic hair. The latter by the time of the menarche has nearly always reached the third stage and is often well along in the fourth stage, whereas axillary hair is usually in the second or third stage.

Age of Occurrence of Menarche and Menses

Many studies of adolescent girls have now been made that include the recording of the age at which the first menstrual period occurred. The average age in the different studies of girls in the United States is about thirteen years, with the range for separate groups between twelve and a half and thirteen and a half years. It appears that this average has become somewhat earlier in recent years and that girls reach the menarche on the average a few months earlier than did their mothers. According to an analysis by Shuttleworth[6] of data compiled by Mills, representing nine geographical areas of the world, girls in the United States menstruate earlier than do those in any of the other regions — two or more years earlier than do those in some of them.

As concerns the range of variability of the time of the menarche within any one group, this occurs in very few girls more than two years before or two years after the age for the average. Thus, for the United

States the range of usual occurrence is between eleven and fifteen years, with about 3 per cent falling below and 3 per cent above these limits. In the main, variations in the time of occurrence of the first menstrual period are closely correlated with variations in other developmental occurrences and may therefore be looked on as due to the speed or advancement of general maturation. The timing of this event occurs quite regularly at or near a particular stage of general development. There is, however, some variability in this respect; that is, girls with extremely early menarches tend to be less mature, and those with extremely late ones more mature in other respects. Greulich et al.[5] suggest that some of the variability in the age of menarche may be due to the same factors that cause irregularities in the early menstrual cycles themselves. He believes that the menarche should be looked on only as a reflection of a general physiologic state, and that it may occur at somewhat different times or stages of pubescent development in different persons.

Engle and Shelesnyak[35] have studied the length and regularity of the menstrual intervals during adolescence. Their findings may be summarized as indicating that the menstrual intervals are considerably longer and much more irregular during the first year after the menarche than subsequently. Girls who menstruate before thirteen years have slightly shorter intervals during both the first and subsequent years than do those who first menstruate after fourteen years. Engle states that variability in cycles decreases as menstrual age increases, and that menstrual regularity is not usually established until twenty to twenty-four cycles have been passed, or until about two years after the menarche. Seventy-eight of 100 girls in his series experienced an interval of more than fifty-seven days, suggesting that menstrual function had been temporarily suppressed or that one period had been missed. In one third of these cases the long cycles were between the first and second periods. Bayer,[36] who has studied the same subject, points out that far greater irregularity occurs between the first two periods than between subsequent ones. She also finds that most girls of feminine build reach the menarche at or near the average age and rarely have unduly long intervals between periods, unduly long periods or severe dysmenorrhea. On the other hand, among the hypofeminine girls — those with a high masculine component of build — and among hyperfeminine ones — those with a low masculine component of build and a high incidence of obesity — these irregularities are more frequent. Severinghaus[37] has discussed from the clinical point of view the relation between these physiologic variables in menstruation and the so-called "menstrual abnormalities" of adolescence.

In describing the development of the sex organs in boys and their functional maturation, it was pointed out above that the precise stage of development at which the capacity to reproduce is attained is not known, but there is probably a considerable period during which some motile spermatozoa are present and hence fertilization may take place but during which sterility appears to be the rule. Attempts to determine how soon after the menarche girls can become pregnant are subject to the same difficulties, except that the menarche can be determined exactly. Mills and Ogle[38] recorded the ages of the menarche and of the first conception in various groups among which promiscuity was frequent from an early age. The lag between the two occurrences was much longer in the girls reaching menarche extremely early than in those reaching it late. Obviously, the former are less likely to be exposed soon after this event than are the latter, but it may also be that the initiation of menstrual cycles does not always occur when reproductive capacity is equally near to attainment. The evidence suggests that conception is extremely unlikely to occur during the first year following the menarche, and that for a period of four to six years it is less likely than after full maturity but does occur with increasing frequency. This period of adolescent or physiologic sterility progressively shortens as the menarche is delayed. Conception can occur very early, but it seldom does so before the age of sixteen, regardless of the age at the menarche.

Mills refers to several animal experiments that tend to confirm the impression of a long period of adolescent sterility. Hartman[39] found that monkeys did not become pregnant until a definite stage of body development had been reached, regardless of how early the menses occurred. The monkeys menstruated on the average when they attained a weight of 3350 gm., but the earliest to conceive weighed 4370 gm., and the average weight at conception was 5000 gm. The interval between these two events was about a year, in spite of frequent matings.

Interrelations between Growth, Osseous Development and Sexual Maturation

In discussing individual variability in growth, it was shown that if chronological age is discarded as the basis for comparing individual children and the time of occurrence of maximum growth is substituted, growth during these years appears to be much more uniform. In like manner if, for comparing children, the age of appearance of one of the sex characters is chosen rather than the chronological age, all persons at this stage are found to be much more alike in other aspects of sexual maturation. As a landmark in this developmental schedule, the menarche in girls is the most definite event that can be selected, much more so than any specific event in the course of maturation in boys. Hence,

all aspects of the growth and development of girls have been studied intensively in relation to the first menstrual period.

Boas[2] in 1932 called attention to the relations between the menarche and growth, but Shuttleworth[19] in 1937 published the first comprehensive analysis

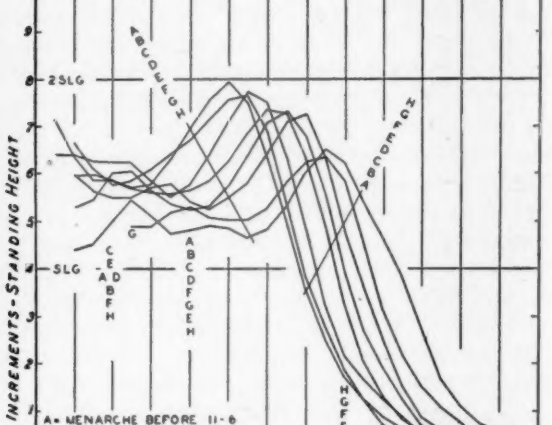
INCREMENTS - STANDING HEIGHT
2 SLG
SLG
A= MENARCHE BEFORE 11-6
B= " 11-6 TO 11-11
C= " 12-0 " 12-5
D= " 12-6 " 12-11
E= " 13-0 " 13-5
F= " 13-6 " 13-11
G= " 14-0 " 14-5
H= " AFTER 14-5
6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 17.0 18.0 19.0
YEARS ENDING AT INDICATED AGES

FIGURE 3. *Average Annual Increments in Standing Height of Eight Groups of Patients Menstruating at Different Ages (reproduced from Shuttleworth,[19] by permission of the author).*

of the growth of girls on the basis of menarcheal age. Using the data collected by Dearborn and his associates in the Harvard Growth Study on a large number of girls whose age at first menstruation was known, Shuttleworth formed eight groups, the first including those who menstruated under ten and a half years and the eighth, those who did so at fourteen and a half years or over. Each intervening group included those who did so within half-year age intervals. He plotted the average curves of growth for each of these groups for different measurements against chronological age. All the curves show a striking similarity in form, but the curve for each advancing age group was displaced further to the right. The first group reached the peak of growth at the earliest age, and each succeeding group reached it a little later. Shuttleworth plotted these same curves on a base line of years before and after the menarche, with the menarcheal ages of all groups superimposed. Under this arrangement the curves for all are much more nearly alike in placement. The striking nature of this relation can best be appreciated by reference to Shuttleworth's graphs, two of which are reproduced in Figures 3 and 4.

Figure 4 shows that there is still some difference between the extreme menarcheal groups in respect to the magnitude of the maximum growth and to its timing. The amount of maximum growth tends to be greater the earlier the menarche. The girls who menstruated earliest reached their peak of growth in height at or slightly after this event, whereas those who menstruated latest did so about a year in advance of it. The intervening groups reached the inflection point in growth between three and nine months before they menstruated. Shuttleworth found the same timing of maximum growth in relation to the first menstrual period held for other body measurements, and even for the small bones of the hand as measured on x-ray films.[12]

Pryor[34] obtained several measurements of girls at half-year intervals over a period of four years, which included the menarche. She found that rapid

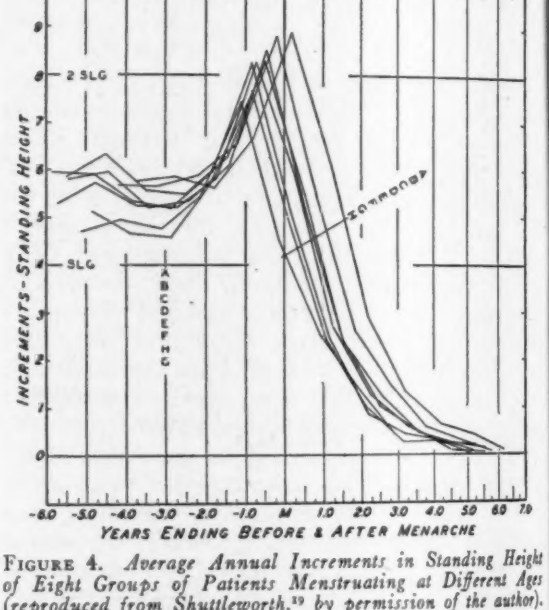

FIGURE 4. *Average Annual Increments in Standing Height of Eight Groups of Patients Menstruating at Different Ages (reproduced from Shuttleworth,[19] by permission of the author). The curves are arranged so that the points corresponding to the advent of the menarche are in the same vertical line.*

gain in height and weight was quite evenly distributed over a period of eighteen months prior to the menarche and continued up to it. Gain in weight was maximum during the last six months of this period.

Simmons and Greulich[40] have published an analysis of their findings in the Cleveland studies of the relation between menarcheal age and height and weight, and these are in close agreement with those of Shuttleworth. They state that the average girl experiences her greatest height increment during the year preceding the year of the menarche, but that some girls do so during that year and some during the second year preceding the menarche. Some girls with late menarches experience little or

no premenarcheal acceleration. Maximum increment in standing height was never found by them to occur after the menarche.

The exact timing of the inflection between accelerating and decelerating growth cannot be determined by measurements taken at yearly or half-yearly intervals. The slight differences in this timing found by different observers are probably due, at least in part, to the intervals of measuring used, but the consensus of all studies is that maximum growth is usually attained shortly before the first menstrual period and that rapidly decelerating growth sets in shortly before or immediately thereafter. It is well established that maximum growth and sexual maturation are closely correlated in point of time, irrespective of differences in age.

Simmons and Greulich are also in agreement with Richey[41] in respect to other relations brought to light by analysis of data for both girls and boys obtained at the Laboratory School of the University of Chicago. Richey separated a series of girls into three groups on the basis of being early, average or late in their first menstrual periods, and boys into three groups on the basis of age of appearance of axillary hair. Girls who menstruated before thirteen years of age were heavier and usually taller at each age from six to seventeen years than were those who did so in their fourteenth year, and even more so than those who menstruated after fourteen years. The same held for boys who showed axillary hair before fourteen years as against those who did so in their fifteenth year, and especially in contrast to those who matured to this extent after fifteen years. There were, however, no significant differences in the average heights of these three groups after adult status was attained — after fifteen years in girls and seventeen years in boys. Richey points out that although the pubescent spurt momentarily increases the differences in the heights and weights of the three groups, the actual differences found at the end of this period are primarily due to long-continued differences in the average growth rates extending well back into childhood. Simmons and Greulich also find that girls with early menarcheal ages on the average have greater weight for height than do girls with late menarches, and that the former have greater accelerations and decelerations in connection with maximum growth. The deceleration of gain in weight is less sharp than that in height.

Stone and Barker[42] found that girls who had reached the menarche averaged three and a half to four and a half growth years, or about fourteen to nineteen pounds heavier, than girls of the same age who had not reached the menarche. The differences in chest and pelvic breadths were somewhat less but in the same direction. Height was also greater in the former group during the early years, but the difference in this respect diminished with advancing years, and as growth came to its end the late maturing girls were actually taller.

Bayley[43] confirmed the general findings outlined above in relation to differences in size and rate of growth between early and late maturing children for boys as well as for girls, using osseous development as the basis for separating the boys into groups. Using bi-iliac diameter and biacromial width in addition to height and weight, she also went further with the analysis of body build in relation to advancement or retardation in maturation. She found that early maturing boys had relatively broad hips at all ages compared with late maturing boys. She also found that early maturing girls had relatively narrow shoulders compared with late maturing girls. This is of interest since early maturation, broad hips and narrow shoulders are feminine characteristics, and late maturation, narrow hips and broad shoulders are male characteristics. Pryor[34] also found that girls of broad body build menstruated earlier than did girls of slender build. Pryor and Carter[44] showed that when comparing broad-built girls with slender-built girls on the basis of anatomical age, — that is, the osseous age determined from x-ray films of the hand, the former had age equivalents greater than their chronological age, whereas slender-built girls had age equivalents less than their chronological age. Physiologic development paralleled anatomic development quite closely. From a practical viewpoint, these studies add further evidence of the advantages to be derived from knowing a child's skeletal as well as his chronological age during the adolescent years.

In considering osseous development it was stated that a characteristic picture is associated with the period of maximum growth, as seen in the hand and elsewhere. It is now apparent that this is also characteristic of the menarche. Flory,[27] studying the x-ray films of the hands of girls in relation to the menarche, found no case in which menstruation occurred before the appearance of the sesamoid at the distal end of the first metacarpal. The average time of its appearance was between one and two years before the menarche. He suggests that the presence of this process may be taken to indicate that menstruation will probably take place within two years if it has not done so already. It is preferable, however, to study the whole hand and if possible other parts, thus assessing the whole pattern of osseous development. If this is done, the osseous rating usually correlates closely with menarcheal age.

Simmons and Greulich found that girls who menstruated early were advanced in skeletal age over the girls in the average menarcheal group, and the latter, in turn, were advanced over those in the late group. Skeletal age was found to be more highly correlated with menarcheal age than was height or

weight, and it gave evidence of early, average or late maturing before the accelerating growth in height sets in. Skeletal age at the menarche, as interpreted on the basis of Todd's norms for the hand, was found to be only half as variable as was chronological age.

Bayley[43] studied various aspects of body build in relation to the rate of skeletal maturation in both girls and boys from ten to eighteen years of age. She formed three groups on the basis of assessment of the hand and knee, representing early, average and late osseous development. This study showed that when height and weight data are plotted on the basis of osseous age, sex differences practically disappear and there is a more consistent pattern of growth than is found on a chronological-age basis.

In the studies of physical competence previously referred to, Espenschade[25] showed that the motor performances of the children studied evidenced positive correlations with anatomic (osseous) age, the menarche in girls and other criteria of physiologic maturity in boys. All these tests of motor function were positively intercorrelated, although less so between gross and fine motor tests than between those in either group. All the intercorrelations were much less significant for girls than for boys.

Greulich and his associates[30] compared the skeletal status of a large number of pubescent boys with the degree of development of their primary and secondary sexual characters. They divided the boys studied into five maturity groups, in accordance with their relative advancement in the latter characters, and compared these groups both with the osseous age and the chronological age. The development of the skeleton tended to keep pace with that of the external sex characters. Within the same maturity group, however, boys who were older chronologically tended on the average to be more mature skeletally than did the younger boys, although they were still somewhat retarded in this respect in relation to their chronological ages.

In this connection it should be pointed out that the menarche is associated with a fairly characteristic stage of development of the secondary sex characters. Pryor finds that it usually occurs when the breasts are in the stage of conical areola protrusion, with primary adipose mammary enlargement, when the pubic hair is long and curly, although less dense than at maturity and when axillary hair is in the second stage. It is for this reason that these stages of pubic and axillary hair development are often selected for comparing boys of supposedly the same stage of development with girls at the menarche. As has been pointed out, the age of maximum growth and an identical stage of osseous development as seen in x-ray films of the hand may also be used as means of pairing boys and girls of comparable development.

(To be concluded)

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CASE RECORDS OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 32211

PRESENTATION OF CASE

A forty-six-year-old carpenter entered the hospital because of abdominal pain and vomiting.

The patient had been in apparent good health until two years before his last admission, when he had a two-day bout of severe crampy periumbilical nonradiating pain accompanied by nausea and vomiting. The pain was sudden in onset and required hospitalization for ten days. It bore no relation to meals and was not relieved by soda or food. He was discharged from the hospital on a diet. Eight months later he had a similar episode, which lasted intermittently for about three weeks and was associated with marked constipation. At that time he also had pleurisy and was hospitalized for one month. After discharge he continued to have a cough and to raise sputum, and for these reasons he was admitted to this hospital. A left lower lobe lobectomy was performed at that time for lung abscesses. While in the hospital he had another attack of abdominal pain. Physical examination of the abdomen, as well as a gastrointestinal series and a barium enema, was negative. Following the chest operation another abscess developed in the lingula, which yielded satisfactorily to penicillin treatment. The patient then gained weight and was completely asymptomatic until the month before admission, when he again had two attacks of periumbilical cramps, followed by vomiting after three to four hours. The pain was severe enough to require sedation with morphine. A Graham test, gastrointestinal series and barium enema, done at a local hospital, were reported as negative. At no time were the attacks accompanied by jaundice, melena, diarrhea or hematemesis. The appetite remained fair.

Physical examination revealed a well developed and well nourished man apparently in no acute distress. The heart was normal. The breath sounds were diminished at the left base. The abdomen was tender to pressure in the lower quadrants, but no masses were felt. Peristalsis was normal and active. The temperature, pulse and respirations were normal. The blood pressure was 128 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 12 gm. per 100 cc. The white-cell count was 7100. The nonprotein nitrogen was 31 mg. per 100 cc. The chloride was 104 milliequiv. per liter, and the total serum protein was 5.8 gm. per 100 cc. The serum amylase was 30 units per 100 cc. The urine was normal. The stools were guaiac negative on repeated examinations.

X-ray examination of the chest showed the mediastinum retracted to the left. The left leaf of the diaphragm was elevated, and the left costophrenic angle was deformed, apparently by old adhesions. Scattered bits of opaque material remained on the left side, and there were several areas in the left lower chest in which the lung markings could not be traced. A flat film of the abdomen showed a large amount of gas and fecal material in the colon. There were also gas-filled loops of small intestine. A gastrointestinal series with hourly films revealed a rounded extrinsic pressure defect of the duodenal bulb, which was probably due to the gall bladder. The stomach emptied normally. There was a peculiar widening and crowding of the mucosal markings in the jejunum that was somewhat suggestive of an intussusception led by a small tumor mass. A later film, however, showed that the head of the barium column was approaching the splenic flexure, with the barium distributed throughout the right colon and ileum. The jejunum was empty on the four-hour film. The ileum appeared wider and lay lower in the pelvis than usual. A small-bowel enema, done to check on the previous findings, failed to show any abnormality.

The patient continued to have occasional attacks of crampy periumbilical pain and nausea. Another flat plate taken during one of the attacks showed several dilated loops of gas-filled small bowel, with only a small amount of air in the colon.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. GRANTLEY W. TAYLOR: May we start off by seeing the x-ray films?

DR. RICHARD SCHATZKI: This is a postoperative film following lobectomy. It shows what was described in the report. These are the films of the gastrointestinal series. The report as stated in the record gives an erroneous impression regarding the permanency of the unusual finding in the small intestine. It was actually seen on only one film. The small intestine is widened locally, and its appearance suggests intussusception. The bowel proximal to it is widened, whereas on the earlier and later films taken on the same day there is no evidence of any abnormality, not even widening of the small intestine. These are the films taken at the time of

the small-bowel enema; the lower jejunum was studied particularly carefully, but no abnormality of any kind was seen. The bowel did not appear dilated. Additional films were taken at half-hour intervals over a period of one and a half hours, and again nothing abnormal was seen. A flat film taken on the next day showed definitely dilated loops of small intestine.

Dr. Taylor: Dr. Schatzki started by showing you the films of the chest, but I shall pass over the lung condition with only a brief comment. It is unfortunate that he developed pleurisy and lung abscesses and had to have an operation, but I cannot see any possible connection between the lung condition and the gastrointestinal tract.

Essentially, we have a patient with recurrent bouts of obstructing pain and vomiting occurring intermittently over a period of years. At the time of his second admission he was described as being a well developed, well nourished man in no acute distress, with slight tenderness in the lower abdomen but no other positive findings. These pains were characterized, at various times, by periumbilical cramps, which were almost invariably associated with vomiting and nausea. At times these attacks recurred at frequent intervals for as long as ten days; but at other times there were periods of remission, when the patient was absolutely free from discomfort and inconvenience, gained weight and was asymptomatic. To me, that type of crampy periumbilical pain, associated with vomiting, is indicative of partial intermittent intestinal obstruction, presumably of the small intestine. The vomiting started fairly promptly after the onset of the pain, and the symptoms eventually passed off by themselves. So we might say that whatever was causing this condition had abated spontaneously at the time of admission. There is nothing in the chart or the recorded appearance to suggest that he had an inflammatory process, such as appendicitis or acute cholecystitis.

The laboratory findings, including the temperature, were strikingly negative. He had a lot of x-ray studies at various times, all of which tended to exempt from suspicion the biliary tree and everything else but the intestinal tract. So we come to the problem of what was causing these intermittent bouts of intestinal obstruction; they appear to have been on a mechanical basis, without impairment of the circulatory state of the bowel. The only evidence that sheds any light on the nature of the process that was doing this is the x-ray observation that Dr. Schatzki has just pointed out. What sort of things do leave a man in good health, with no abnormal laboratory findings, with intermittent bouts of certainly distorted bowel but without actual obstruction of the bowel? We always have abnormal bands and kinks and that sort of thing to consider. Since there had been no previous operation, artificially made adhesions could not have caused these attacks. There is no description of a hernia. O course, internal hernias are not infrequent, but the do not repeatedly resolve themselves in this fashio without active therapeutic intervention. Meckel' diverticulum is often associated with this type o symptomatology, but there is nothing in the pro tocol that justifies making the assumption that tha condition was present. So we come to the problem of the x-ray condition, whatever it is, as an explanation of his symptomatology. The x-ray people are certainly "handing it to us on a platter" when they say, "There was a peculiar widening and crowding of the mucosal markings in the jejunum that was somewhat suggestive of an intussusception led by a small tumor mass." Even without such a gratuitous offering I think that we might arrive at the conclusion that some such condition was present. Certainly if we entertain the idea of tumor it seems to me that the condition of the patient in relation to the duration of symptoms argues against the presence of malignant neoplasm. When it comes to deciding what sort of benign neoplasm was involved, a histologic examination is required. There are leiomyomas, fibromas, lipomas and other rarer tumors of the small intestine. Someone will say, "What about lymphoblastoma?" That often behaves like a benign tumor in its leisurely progress, with freedom from hemorrhage and cachexia for some time, but after two years' duration there should have been evidence of lymphoblastoma elsewhere.

I cannot do more, Dr. Mallory, than to say I believe that this patient had a primary neoplasm of the small intestine, probably benign, the histologic character of which I leave to you. He may have had a dyskinesia that justified the diagnosis of intussusception. Certainly, if he had an intussusception, it resolved itself without gross blood or pronounced clots in the stools, both of which are traditions in intussusception.

Dr. Tracy B. Mallory: Dr. Herrera, will you describe what was seen when the abdomen was first opened?

Dr. Rodolfo E. Herrera: We operated because we were convinced that he had had repeated episodes of small-bowel obstruction. When we opened the abdomen, we found throughout the mesentery and omentum innumerable small pale-yellow granules; some of the nodes of the mesentery, in fact most of them, were enlarged and felt soft. In only one region — the midjejunum — was there any invasion of the small bowel. This area somewhat resembled regional enteritis, with thickening of the mesentery and invasion of the bowel wall causing almost complete obstruction. There was great disparity between the size of bowel proximal and distal to this loop. Because of the extent of the process in the mesentery we did not believe that we could cure him, and we entertained the diagnosis of lymphoma or tuberculosis at that time. To establish the diag-

nosis conclusively and also since the region of the jejunum seemed to be irreversibly obstructed, we resected the jejunum and did a side-to-side enteroenterostomy.

DR. MALLORY: Would you care to add anything at this point, Dr. Taylor?

DR. TAYLOR: Not a thing. The case is very instructive.

CLINICAL DIAGNOSES

Recurrent intestinal obstruction.
Granuloma, small bowel.

DR. TAYLOR'S DIAGNOSIS

Benign tumor of jejunum.

ANATOMICAL DIAGNOSIS

Malignant lymphoma (giant-follicle type) of jejunum, mesentery and omentum.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The pathologist was called in consultation in the midst of the operation. The first specimen was a piece of the omentum, and frozen sections showed a picture that I never happen to have seen before — many isolated lymphoid follicles, all of which were quite separate from one another. We thought at the time that it was a lymphoma of the so-called "giant-follicle type," although we had never seen a manifestation quite like this. When the resected specimen was brought over to the laboratory, a tumor mass was found, as Dr. Herrera has told you, in the small bowel and the adjacent mesentery. Sections of that showed obvious and typical lesions of giant-follicle lymphoma. As perhaps you know, of all the types of lymphoma this is the one that ordinarily runs a relatively benign course. A duration of two years without generalized cachexia is not impossible with this type of lesion. I think that it is fair to assume that this is what he had from the start of his intestinal symptoms. I doubt that it can be tied in in any way with the chest disease.

DR. SCHATZKI: After we knew the cause of the patient's trouble, we went back over the films to see if we could find any evidence of the disease. I could see what appeared to be a tumor on only one film, which was taken at the time the mass had intussuscepted and had produced obstruction. When you know that there is something, it is rather discouraging to look carefully for it and still be unable to demonstrate it.

DR. MALLORY: This man, of course, will get x-ray treatment, and the prognosis is relatively good. The average duration of this type of disease is nearly five years from the onset of symptoms, and he might easily live a number of years in an excellent state of health. We believe, in this hospital, that when there is a lymphomatous involvement of a hollow viscus it is wise to resect it before initiating x-ray treatment. There is significant danger of spontaneous perforation of the lesion if x-ray treatment is started too vigorously when the intestinal tract is involved. Do you agree, Dr. Schatzki?

DR. SCHATZKI: We have become more courageous but still advocate surgery if it can be done. A single lesion probably offers the best prognosis.

DR. HERRERA: I should like to ask Dr. Schatzki whether he thinks that the diagnosis might have been established if, instead of doing a small-bowel series in the usual way, they had allowed the Miller–Abbott tube to advance and had introduced barium through it.

DR. SCHATZKI: That would have offered a good chance, unless the Miller–Abbott tube had gone through the area of narrowing.

DR. HERRERA: I do not believe that it could have gone through.

CASE 32212

PRESENTATION OF CASE

A sixty-five-year-old Italian mother of ten children entered the hospital because of abdominal pain, nausea and vomiting.

The patient had been in good health until one year prior to entry, when she began to complain of mild upper abdominal discomfort coming on usually in the evening and after meals. There was no vomiting, diarrhea, chills or jaundice. Ten days before entry, following a supper of ice cream and pie, the patient complained during the night of nausea and slight pain in the right lower quadrant, which became generalized by the following morning. She also began to vomit and pass profuse watery stools. After taking some pills prescribed by her local physician, the symptoms abated somewhat but the pain and vomiting of everything taken orally continued until admission.

Physical examination showed a well developed and well nourished woman in no acute distress. The tongue was dry and reddened. The chest was clear except for a few transient rales at the right base. The abdomen was evenly protuberant, soft and nontender. Peristalsis was active. No masses were felt.

The blood pressure was 198 systolic, 108 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a white-cell count of 12,700, with 82 per cent neutrophils. The hemoglobin was 14 gm. per 100 cc. The serum bilirubin was 0.85 mg. per 100 cc. direct, and 1.0 mg. indirect. The total protein was 5.4 gm., per 100 cc., with an albumin-globulin ratio of 2.5. The chloride was 101 milliequiv. per liter, and the nonprotein nitrogen 16 mg. per 100 cc. A blood Hinton test was negative. The urine was normal. A stool was guaiac negative.

X-ray examination of the chest showed considerable increase in the markings throughout the lung fields, with a few nodular areas well out toward the periphery. The heart was within normal limits, and the aorta was tortuous. A plain abdominal film showed multiple dilated loops of small bowel and a large amount of gas and fluid in the cecum, ascending and transverse colon. A barium enema showed barium passing readily into the large bowel and into the region of the cecum. No defects were noted, but the preparation of the patient was not satisfactory. The barium was poorly evacuated. Multiple irregular faceted areas of calcification having the typical appearance of gallstones were found in the right upper quadrant. A Graham test showed rather poor concentration of the dye, but the gall bladder contracted fairly well after a fat-containing meal.

A Miller–Abbott tube was passed, which resulted in gradual decompression and improvement in the patient's condition. On the third hospital day a flat film showed the tip of the tube well down in the pelvis. There were still several loops of dilated small bowel. On the sixth hospital day another flat film of the abdomen showed a suggestion of a filling defect at the hepatic flexure of the colon, with dilatation of the cecum and ascending colon up to that point. A large gas bubble seemed to be in or near the gall bladder.

On the twelfth hospital day another barium enema was administered. The barium met a complete obstruction in the ascending colon close to the hepatic flexure. Fluoroscopically it was thought that the upper margin of the obstruction was shelf-like, but not enough barium passed the point to be certain of the type of lesion.

An intravenous pyelogram performed on the thirteenth hospital day revealed normally functioning kidneys and a soft-tissue pelvic mass, which appeared to be somewhat lobulated and compressed the bladder.

On the fourteenth hospital day an operation was performed.

Differential Diagnosis

Dr. Lamar Soutter: This woman came in with a story that sounds like intestinal obstruction. At the time of her operation, twelve days after entry, x-ray studies were again indicative of obstruction. Let us look first at the x-ray films.

Dr. Richard Schatzki: Unfortunately the first film of the chest and the films of the first barium enema are not available. I was told by the man who examined the patient at the time of the first barium enema that the examination was unsatisfactory owing to a large amount of fecal material.

These are the two flat films with the Miller–Abbott tube in place; the retained barium is mainly in the transverse colon, the region of the ascending colon being filled with air. The Miller–Abbott tube had passed through the small intestine and is apparently just trying to negotiate the ileocecal valve; possibly it has already passed through the valve. This is the film taken at the time of the second barium enema, and you can see the obstruction just proximal to the hepatic flexure in the upper ascending colon. The obstruction is complete; no barium passes beyond the point of obstruction. Here you see the gallstones. The intravenous pyelogram may be of interest because it shows a soft-tissue mass that is pushing the bladder downward.

Dr. Soutter: When we go back over the history we find that the patient had been in good health until a year before entry, when she began to complain of mild upper abdominal discomfort coming on usually in the evening after meals. Upper abdominal discomfort, of course, does not give us much information. It is compatible with gallstones and chronic cholecystitis, which she has. On the other hand, the symptoms at that time were vague and could have been caused by many things. Can the entire story be explained on the basis of an inflamed gall bladder that was obstructing the ascending colon and the small bowel. In the first place, the acute onset of her disease, ten days before entry, does not lead one to believe that it was due to gall bladder trouble. There was not the typical pain with radiation to the back. She had profuse watery stools and a lot of vomiting, but little evidence of inflammation. She had only a slightly elevated white-cell count, and there was no fever, no tenderness, and no mass. Furthermore, the Graham test done a few days after entry showed that the gall bladder did not fill well, which is compatible with chronic cholecystitis and cholelithiasis, but it emptied well, which is incompatible with an acutely inflamed gall bladder. Therefore, we can say that at the time she came in the symptoms were probably not related to the gall bladder.

Could she have an intrinsic lesion in the colon that was causing obstruction but was relieved only to recur again in the hospital? She had no anemia. The serum protein was slightly depleted, with a normal albumin-globulin ratio, but the protein can be depleted in a person who has been vomiting for ten days and who has had profuse watery stools. The watery stools suggest that, if she had obstruction, it was not complete. Subacute obstruction will often give diarrhea. It is therefore possible that she came in with a lesion of the ascending colon at the hepatic flexure or just below it that was causing obstruction, which was relieved during the stay in the hospital. Why did that not show up at the time of the first barium enema? As Dr. Schatzki has told us, this was an unsatisfactory procedure, owing to a lot of gas and feces, and the growth that could have caused temporary obstruction would not necessarily have been visualized at that time.

Why did the bowel not empty promptly after the barium enema? That is readily explained on the basis of irritation to the bowel from previous obstruction, so that at the time of entry she had ileus, paralytic in nature, secondary to obstruction. In other words, although the obstruction was temporarily relieved, as shown by the fact that the barium passed into the cecum at the time of the first barium enema, the bowel did not empty because it had not regained its tone.

Could she have had an extrinsic inflammatory lesion that subsequently obstructed the bowel? There again the hospital course is against it. It is possible that she had an acute cholecystitis following the cholecystogram. Occasionally an acute gall bladder becomes adherent to the omentum and so forth and obstructs the colon because of inflammatory adhesions. We do not know enough about the hospital course to say whether an inflammatory process was going on. It is not suggestive, however, and I shall therefore presume that it did not occur. We have no lead that she had difficulty with the right kidney. Since she had a normal pyelogram, it is likely that no renal tumor was pressing on the colon. The history is not particularly suggestive of an ulcer of the duodenum that had perforated, thus producing this obstruction.

Could she have had a lesion a little higher up in the intestines? If she had an obstruction before entry, which is probable, it could well have been a small-bowel obstruction that was not complete. What could have given a partial obstruction in the small bowel that was later relieved? This could have been caused by some growth at the ileocecal valve, probably one that projected or pressed into the lumen of the bowel and produced partial obstruction, with subsequent relief when it came out of the lumen. Along that line we think of such things as adenoma, leiomyoma, lipoma and so forth. There could well have been a certain amount of gas and feces in the cecum from paralytic ileus if the obstruction was above this level. We do not know why the second barium enema was given. It was apparently done because the patient again had obstructive symptoms. The fact that the barium failed to pass beyond the hepatic flexure, with a fleck of barium projecting out there, is suggestive that this was due to a growth at that level with complete obstruction; but she could also have had a growth at the ileocecal valve with intussusception up to the level of the hepatic flexure, so that the barium failed to go farther. Against intussusception is the fact that the stool was guaiac negative. Intussusception, however, is fairly rare in adults, particularly women, and it is nearly always associated with blood in the stool. We do not know whether she had blood in the stool at the time of the second enema, but she could perfectly well have had a small-bowel lesion that had intussuscepted into the colon because it lay close to the ileocecal valve.

The intravenous pyelogram is interesting. The most frequent cause of a fairly well outlined pelvic mass pressing into the bladder in a woman who has passed the menopause with no particular story of pelvic difficulty is a fibroid uterus. It is difficult to visualize any obstructive lesion of the descending colon that would interfere with the bladder without there being a definite palpable mass. Furthermore, without signs of obstruction at that level at the time of the two barium enemas, the lesion appears to have been higher. Further suggestive evidence of a lesion in the small bowel, rather than one in the large bowel, is the fact that the vomiting came on almost immediately. With a polypoid type of growth obstructing the small bowel, one would expect vomiting earlier than if she had had obstruction at the hepatic flexure.

In conclusion I shall say that this woman's lesion was neoplastic, that it was probably benign, because of the blood picture and history, that she had temporary obstruction prior to coming in, which was relieved on entry, that the lesion was probably in the region of the ileocecal valve and that she had intussusception at the time that the second barium enema was taken. It is, of course, impossible to exclude a neoplastic lesion at or just below the hepatic flexure.

Dr. Schatzki: Against intussusception is perhaps the fact that in the film you can see air in what appears to be a normal cecum.

Clinical Diagnoses

Cholelithiasis?
Carcinoma of large bowel.

Dr. Soutter's Diagnosis

Benign tumor of ileocecal valve, with intussusception of ileum into cecum and ascending colon.

Anatomical Diagnosis

Adenocarcinoma of ascending colon.

Pathological Discussion

Dr. Tracy B. Mallory: This patient was operated on by Dr. Langdon Parsons. I am sorry that he is not here to describe the operative findings. He found a tumor in the ascending colon, and resected it, together with a small portion of the terminal ileum. The specimen that we received showed a carcinoma of the ascending colon at about its midportion; it was 5 or 6 cm. from the ileocecal valve and 13 cm. from the edge of the resection. There were a few enlarged lymph nodes in the attached mesentery, but these were histologically free from metastases. If an intussusception had been present, there was no trace of it at the time of operation.

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DOSAGE OF PENICILLIN

THERE is considerable confusion in the minds of most physicians about the dosage of penicillin in the treatment of various infections. This is due in part to the fact that the early studies on penicillin therapy were made when the material was quite scarce, as a result of which attempts were made to define the dose in terms approximating the minimum effective amount. When the supply of the antibiotic became more plentiful, the trend was in the opposite direction, large doses being advocated and used empirically. Some justification for the large doses was found in the better results achieved in such conditions as subacute bacterial endocarditis and other infections in which small doses had failed to produce a satisfactory clinical response. A knowledge of the factors determining the optimum dose to be used in any given set of circumstances, however, is essential if one is to provide adequate therapy and at the same time to avoid ridiculous waste of large amounts of this valuable material.

The factors determining the dosage of penicillin in infections have been recently reviewed by Rammelkamp and Kirby.* These authors point out that there is a closer correlation with penicillin than with sulfonamides between the sensitivity of bacteria in vitro and the clinical results obtained. This is attributed in part to the fact that sulfonamides are inhibited by substances contained in pus and exudates, whereas the same is not true of penicillin. Penicillin is selective in its activity. For the most part, this selectivity refers to the high degree of antibacterial action of penicillin against gram-positive bacteria and its failure to inhibit the growth of most gram-negative bacteria. There is considerable variation, however, in the degree of sensitivity of different bacteria and even of different strains of the same organism. For practical purposes, however, most of penicillin-sensitive bacteria that are frequently encountered, particularly the gonococcus, pneumococcus and beta-hemolytic streptococcus, exhibit variations that are not of sufficient clinical significance to affect the results of therapy. In cases of subacute bacterial endocarditis and in certain staphylococcal infections, on the other hand, there may be wide variations in the sensitivity of the etiologic organisms. It is only in the latter types of cases, therefore, that a knowledge of the sensitivity of the organism may be of importance both from the standpoint of therapy and that of prognosis.

The problem of acquired resistance or fastness of bacteria has received intensive study because of the importance of that feature in relation to sulfonamide therapy. It has been shown that most of the penicillin-susceptible organisms develop resistance only after prolonged exposure to the antibiotic. Clinical experience has indicated that, with the exception of the staphylococcus, well substantiated instances of penicillin resistance acquired during therapy have been rare. Furthermore, in certain cases of streptococcal, pneumococcal and

*Rammelkamp, C. H., and Kirby, W. M. M. Factors determining dosage of penicillin in treatment of infections. *Bull. New York Acad. Med.* 21:656-672, 1945.

staphylococcal infections in human beings in which relapses have occurred because of localized infections, penicillin therapy has often been continued for long periods without the development of any measurable degree of penicillin resistance. Although it is too soon to draw any conclusions on this point, the evidence so far available suggests that, except for staphylococcal infections, penicillin resistance will probably not be of any great clinical importance.

The absorption and excretion of penicillin and its diffusion into various body fluids are the next important features to be considered. After intramuscular injections, absorption of penicillin is rapid, the maximum level being achieved within fifteen to twenty minutes. Thus, it is entirely unnecessary and superfluous to begin therapy with a single intravenous dose, as many physicians are inclined to do. After the drug is absorbed, it is rapidly eliminated, so that 80 per cent of the intramuscular dose appears in the urine within the first two hours, and less than 5 per cent remains after four hours. The rapid absorption and rapid elimination of penicillin are therefore responsible for the greatest disadvantage of penicillin therapy at present, namely, the necessity for frequent parenteral injections. Of the many methods used in attempts to delay absorption, Rammelkamp and Kirby consider the intramuscular injection of penicillin in beeswax-peanut oil mixtures to be the most promising. Effective blood levels can be maintained for as long as twenty-four hours after 300,000 units of penicillin given in 1 cc. of such a mixture.

Concerning oral preparations, these authors consider that none of the enteric coatings, oils or antacids thus far employed give better results than those obtained with the ingestion of penicillin dissolved in tap water. With any of these preparations, five or six times as much penicillin must be administered to produce levels equivalent to those obtained following parenteral injections. It is worth mentioning that even this ratio is valid only when the penicillin is given before meals, since in most persons little or no penicillin is absorbed if it is given orally within a short time after the ingestion of food.

The diffusion of penicillin into body fluids and cavities occurs irregularly and generally only to a small extent. For this reason, local therapy as well as parenteral treatment is usually necessary in the treatment of infections of the pleura, pericardium and joints. In some localized infections, such as well established empyemas, parenteral injections are unnecessary, favorable results often being obtained by local injections alone. In meningitis, although there are reports of a few patients who have been cured by parenteral penicillin alone, clinical experience has shown that others have failed to respond to such treatment. In some cases, moreover, bacterial meningitis has actually appeared during parenteral treatment of extrameningeal infections. Penicillin should therefore be given both parenterally and intrathecally in cases of meningitis. There are two notable exceptions. In cases of syphilitic meningitis, excellent results have been obtained with intramuscular penicillin, and in cases of meningococcal infections, systemic sulfonamide therapy is usually adequate and probably more effective than treatment with penicillin given both intrathecally and parenterally.

In certain conditions, notably subacute bacterial endocarditis, various forms of late syphilis and chronic osteomyelitis, the factor of penetration is extremely important. Favorable results can be obtained and relapses avoided only by the maintenance of high blood levels continuously for long periods.

MASSACHUSETTS MEDICAL SOCIETY
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The Postwar Loan Fund has been set up, and all discharged medical officers who were members of the Massachusetts Medical Society in good standing at the time of their entry into the service may apply for loans from this fund. For further information apply to:

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Rammelkamp and Kirby also emphasize the fact that, although penicillin is highly effective against the organisms present in the throat in patients with tonsillitis and pharyngitis, lasting beneficial effects are exerted only when penicillin is given parenterally. Local therapy with gargles or sprays is ineffective. After intramuscular injections, however, streptococci disappear or rapidly diminish, but they reappear if treatment is discontinued too soon. It has been definitely demonstrated that, in order to obtain a permanent cure in cases of streptococcal sore throat, it is necessary to continue treatment for five or more days. In pneumococcal pneumonia, too, it is necessary to continue treatment for several days after apparent recovery to ensure sterilization of the infected tissues and to prevent relapse. It is possible that final recovery is brought about in these cases and in certain other infections with the help of the body's own defense mechanisms.

The frequency with which doses are given depends, of course, on the time during which effective levels must be maintained. Rammelkamp and Kirby present evidence that indicates that some antibacterial effect persists after the time when penicillin is no longer demonstrable in the serum by the usual tests. Doubling the size of the dose produces a blood level that is twice as high, but the effective level is prolonged by only one third. The high levels that result from the use of extremely large doses are usually well in excess of those necessary to exert the maximal antibacterial effect. Injections of 20,000 units produce levels in the blood that are considered to be maximum against the staphylococcus for less than one hour, although definite bacteriostasis probably persists for another two hours. For the hemolytic streptococcus, on the other hand, the same dose produces concentrations that have maximum antibacterial action for more than two and a half hours and partial inhibitory levels for another one and a half to two hours. Other factors of importance in determining the size of the dose of penicillin are the severity of the infection, the vascularity of the areas involved and the barriers through which penicillin must diffuse or penetrate to come in contact with the infecting organism.

On the basis of all these factors it is possible to plan rational schemes of treatment. In staphylococcal infections, for example, 25,000 units every two hours will provide optimal levels continuously in the blood stream; for streptococcal infections, 15,000 units every three hours are adequate for this purpose. Two points are especially emphasized. One is that doses producing optimal concentrations of penicillin in the blood stream are all that are necessary. Although larger doses raise the concentration of penicillin, they do not increase the already maximum antibacterial activity and are therefore wasteful. The other point is that, for all practical purposes, penicillin remains active in the tissues for only three, or at most four, hours after the usual therapeutic dose. The use of penicillin at intervals longer than four hours is therefore potentially dangerous, even though occasional infections due to highly sensitive bacteria may respond favorably to doses given at wider intervals.

EFFECT OF VITAMIN SUPPLEMENTS

Our British cousins, a little less enthusiastic than ourselves, who are a mixture of various races although speaking a similar tongue, seem inclined to take their vitamins with a grain of salt. It is not that they are any less serious about them; it is rather that, conservatively, they seem to prefer them from an apothecary's shop than a slot machine and are even inclined to doubt that health improves in direct proportion to the amount of vitamin concentrate assimilated.

As recently as February, 1946, Bransby, Burns, Magee and MacKecknie* published the results of a study on the effect of a daily vitamin supplement on the health and development of children. The test was made on 1620 children, aged five to fourteen years, attending day schools in the towns of Stoke-on-Trent and Salford. The subjects were divided into the conventional two groups at random, one of which received a daily placebo and the other a capsule containing 4000 int. units of vitamin A, 1 mg. of vitamin B_1, 2 mg. of riboflavin, 20 mg. of nicotinamide, 50 mg. of ascorbic acid and 600 int. units of

*Bransby, E. R., Burns, J. L., Magee, H. E., and MacKecknie, D. M. Effect of daily vitamin supplement on health and development of children. *Brit. M. J.* 1:193-197, 1946.

vitamin D. The tests, which ran for a year, were similar in the two towns but not identical. In Stoke medical, dental and anthropometric data were collected three times during the year, and in Salford twice; in Salford facts were gathered on the economic condition of the subjects; in Stoke dynamometer and hanging-bar tests were performed, and in Salford hearing was tested by means of the audiometer.

The results were essentially nil — a temporary disappointment, no doubt, to the vitamin enthusiasts and faddists: the vitamin supplement had no apparent consistent effect "on growth, strength, endurance, fatigue potential, incidence or severity of clinical conditions, hearing and absenteeism from school.... The vitamin supplement had a beneficial effect on gingivitis in Stoke but not in Salford."

These British experiments, it is true, did not elaborate on all the developmental, nutritional and clinical factors that could have been affected by vitamin therapy, nor did they attempt to measure the incalculable *joie de vivre* that might have resulted from such regular indulgence in these encapsulated cocktails, or to initiate any manner of "shock therapy" by the use of massive doses, such as has been done effectively for certain particular purposes. On the basis of their findings, however, the authors suggest that the recommended vitamin requirements of the National Research Council of the United States are too high, with particular reference to ascorbic acid, that the amounts contained in the average diet are sufficient for the maintenance of satisfactory health and that, consequently, the need for supplemental rations has been exaggerated. These results, however, are only suggestive. We must continue to remember that there is a great deal more to normal nutrition than an adequate vitamin intake and that, contrary to a growing popular belief, supplementary vitamins do not constitute a complete, concentrated diet.

MASSACHUSETTS MEDICAL SOCIETY

EXECUTIVE COMMITTEE OF THE COUNCIL

On April 24, 1946, the Executive Committee of the Council, on the recommendation of the Committee on Membership and representatives from the supervising cen ors, took the following actions:

Allowed the following named fellows, applying for retirement and with all dues paid and in good standing, to retire under the provisions of Chapter I, Section 5, of the by-laws.

Bartlett, William B. (Middlesex South), 28 Monument Street, Concord.
Beals, Lester H. (Franklin), 701 Plymouth Road, Claremont, California.
Bigelow, Enos H. (Middlesex South), 65 Edgell Road, Framingham Centre.
Boutwell, Horace K. (Norfolk), 15 Green Street, Brookline.
Bremer, J. L. (Suffolk), 113 Marlboro Street, Boston.
Canavan, Myrtelle M. (Norfolk), 2061 Dorchester Avenue, Boston.
Draper, Alexis L. (Norfolk), 1107 Washington Street, Dorchester Centre.
Duckering, Florence W. (Suffolk), 483 Beacon Street, Boston.
Grant, Justin F. (Suffolk), 587 Tremont Street, Boston.
Higgins, George V. (Norfolk South), Corner Main and Warren streets, Randolph.
Hollister, F. M. (Plymouth), South Duxbury.
Holt, William L. (Hampshire), Amherst.
Merritt, S. Virgil (Bristol South), 297 Osborn Street, Fall River.
Page, Calvin G. (Suffolk), 128 Marlboro Street, Boston.
Phelps, John S. (Essex South), 768 Boston Street, Lynn.
Schirmer, J. Walter (Suffolk), 85 Lawton Road, Needham.
Tilden, Irving N. (Bristol South), Mattapoisett.
Tyler, Winsor M. (Middlesex South), 1482 Commonwealth Avenue, Brighton.

Allowed the following named fellow, applying for retirement but who is in arrears of dues for the year 1945, to have his dues for the year 1945 to the Massachusetts Medical Society remitted under the provisions of the by-laws, Chapter I, Section 6, and then to retire under the provisions of Chapter I, Section 5, of the by-laws.

Walsh, John E. (Suffolk), 238 Beach Street, Revere.

Allowed the following named fellows, applying for resignation with all dues paid and in good standing, to resign under the provisions of Chapter I, Section 7, of the by-laws.

Adler, Alexandra (Suffolk), Duke University, Durham, North Carolina.
Finnegan, William F. (Non-Resident), 380 North Eighth Street, Lebanon, Pennsylvania.
Haskell, C. D. (Non-Resident), 141 S. Meridian Street, Indianapolis, Indiana.
Hyde, Fritz C. (Non-Resident), 320 East 72nd Street, New York City.
Joy, Genevieve L. (Non-Resident), 202 South Palouse Street, Walla Walla, Washington.
Leone, Joseph P. (Norfolk South), Quincy City Hospital, Quincy.
McMackin, John V. (Non-Resident), 406 Huntington Building, Miami, Florida.
Redlich, Frederick C. (Non-Resident), 333 Cedar Street, New Haven, Connecticut.
Staples, O. Sherwin (Norfolk), Hitchcock Clinic, Hanover, New Hampshire.
Yahn, George W., III (Suffolk), P. O. Box 38, Camarillo, California.

Allowed the following named fellows, applying for resignation from the Massachusetts Medical Society but who are in arrears of dues, to have these dues owed the Massachusetts Medical Society remitted under Chapter I, Section 6, of the by-laws and then to resign from the Massachusetts Medical Society under the provisions of Chapter I, Section 7, of the by-laws.

Forster, Francis M. (Norfolk), 1025 Walnut Street, Philadelphia, Pennsylvania.
Ruesch, Jurgen (Middlesex South), University of California Medical School, The Medical Center, San Francisco, California.

Allowed the following named fellows to change their membership from one district society to another, without change of legal residence, under the provisions of Chapter III, Section 3, of the by-laws.

Bayles, Theodore B., 94 Summer Street, Weston (Middlesex South to Suffolk).
D'Errico, Emilio, 14 Everett Avenue, Winchester (Remain in Middlesex South).
Hanson, Wm. T., 30 Bellevue Road, Stoneham (Remain in Plymouth).
Hare, Hugh F., 66 Fountain Street, West Newton (Middlesex South to Suffolk).
Newell, John L., 35 Walnut Place, Brookline (Norfolk to Suffolk).
Shain, Arthur I., 63 Bay State Road, Boston (Suffolk to Norfolk).
Thorn, George W., 983 Memorial Drive, Cambridge (Middlesex South to Suffolk).
Warren, Richard, 30 Heath Street, Brookline (Remain in Suffolk).

Reinstated the following named physicians, who have been deprived of membership for the nonpayment of dues, provided their arrears in dues at the time of deprivation both to the Massachusetts Medical Society and to their district societies, plus current year dues both to the Massachusetts Medical Society and to their district societies be sent to the Treasurer of the Society, in accordance with Chapter I, Section 10, of the by-laws.

Bennett, Max (Bristol North), 176 County Street, Attleboro.
Gilbert, Meyer M. (Worcester), 30-A Boynton Street, Worcester.
McDonald, J. F. (Worcester North), Main Street, Ashburnham.
O'Brien, John Francis (Middlesex North), 77 Payson Road, Brookline.
Tynan, J. P. (Suffolk), 801 Broadway, South Boston.

Allowed the following named fellows, who have been ill for a number of years and totally disabled or who have been totally disabled through military service, to have their dues to the Massachusetts Medical Society remitted in the future as long as they are permanently disabled and unable to carry on medical practice and duties under the provisions of Chapter I, Section 6, of the by-laws.

Champ, Anthony M. (Plymouth), 109 Manomet Street, Brockton.
Hendry, John J. (Suffolk), 681 Mountain Avenue, Revere.
Krieger, William L. (Norfolk South), 15 Lincoln Avenue, Wollaston.
Sawyer, Alpha R. (Norfolk), 79 Poplar Street, Roslindale.
Sweeney, William J. (Middlesex East), 4 Avon Street, Wakefield.

Allowed the following named fellow, who was deprived of membership in the Massachusetts Medical Society in 1942 on recommendation of the Committee on Membership to the Executive Committee, to be restored to active membership in good standing under the provisions of Chapter I, Section 10 of the by-laws. Former deprivation of fellowship was recommended because of nonpayment of dues. No information was obtained that he was in active military service.

Quigley, Thomas J. (Suffolk), 1633 Tremont Street, Boston.

The personnel of the Committee on Membership is as follows: Harlan F. Newton, *chairman*; Roy V. Baketel; William A. R. Chapin; Peirce H. Leavitt; and Samuel N. Vose. The representatives of the supervising censors were as follows: William H. Allen; H. Quimby Gallupe; and Albert E. Parkhurst.

MICHAEL A. TIGHE, M.D., *Secretary*
Executive Committee

DEATHS

JACK — Lewis H. Jack, M.D., of West Newton, died May 3. He was in his seventy-fourth year.

Dr. Jack received his degree from Harvard Medical School in 1899. At various times during his medical career he was associated with the Boston City, Boston Lying-in, Long Island, Waltham, Winchester and Cambridge hospitals. He had been a member of the staff of the Newton-Wellesley Hospital for twenty-six years. He was a fellow of the American Medical Association.

A son, four daughters and a sister survive.

McLEOD — Melvin S. McLeod, M.D., of Melrose, died February 26. He was in his fiftieth year.

Dr. McLeod received his degree from the University of Vermont College of Medicine in 1920.

His widow and two sons survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PERSONNEL NOTES

William J. Welch, M.D., has been appointed physician-in-chief of the Mobile Blood Donor Unit of the Division of Biologic Laboratories, Massachusetts Department of Public Health. Dr. Welch, who served for two years in the European Theater of Operations as a captain in the Army Medical Corps, has charge of the organization and technical operation of the field team that collects the voluntary blood donations.

Donald A. Martin, M.D., has been appointed director of the Massachusetts Hospital and Health-Center Survey Program. The survey was launched by Governor Tobin for the purpose of studying existing hospital and health facilities in anticipation of passage of the Hill–Burton Bill (S. 191). Prior to his appointment, Dr. Martin was acting superintendent of the Lakeville State Sanatorium in Middleboro.

Robert E. Ober, M.D., epidemiologist with the Division of Communicable Diseases, Massachusetts Department of Public Health, has returned to duty following twenty-nine months overseas service with the Mediterranean Allied Air Forces.

Robert A. MacCready, M.D., recently discharged from the Army Medical Corps, where he held the rank of major, has returned to the Massachusetts Department of Public Health as epidemiologist in the Division of Communicable Diseases. He will be in administrative charge of the Laboratory Approval Program.

Mary Carr Baker, formerly supervisor of public-health education, Massachusetts Department of Public Health, is now field program supervisor of the new Blood Program. As field representative, Mrs. Baker supervises collaborative activities between the department, the American Red Cross and community organizations in arranging for local participation in the Blood Donor Service.

Philip W. Johnston, Ph.D., has returned to the Division of Maternal and Child Health as research consultant in Field Service in Child Growth and Development, his duties including the preparation and validation of tests of vision and hearing for school children. During the war, Dr. Johnston held the rank of lieutenant in the United States Naval Reserve. He was first attached to the Bureau of Naval Personnel as a psychologist but later spent eighteen months in the Pacific area as radar officer on the U. S. S. *Boston*.

Leon A. Alley, M.D., has returned from duty in the European Theater of Operations as a lieutenant colonel after having served five years in the Army Medical Corps. He will resume his position as superintendent of the Lakeville State Sanatorium in Middleboro.

Elizabeth E. Barry, R.N., B.N., has been appointed supervising instructor in public-health nursing (pediatrics), Bureau of Public Health Nursing, for the Rheumatic Fever Program, which is soon to be established in the Massachusetts Department of Public Health. She is a graduate of Yale University School of Nursing and Massachusetts State College.

Jane Y. Harshberger, R.N., M.A., a graduate of Yale University School of Nursing and of the University of Pennsylvania, has recently joined the staff of the Bureau of Public Health Nursing as supervising instructor in public-health nursing. She is conducting an educational program in maternity nursing for public-health and hospital nurses.

MISCELLANY

DEDICATION AT McLEAN HOSPITAL

On May 17, the Scientific Research Laboratory of the McLean Hospital at Waverley, a unit of the Massachusetts General Hospital, was dedicated. The morning program included talks by Dr. C. K. Drinker and Dr. Jordi Folch. Following luncheon and inspection of the laboratory, addresses were given by Dr. Stanley Cobb, Dr. Herbert S. Gasser, of New York City, and Dr. Wilder Penfield, of Montreal. At the reception and dinner, held at the Harvard Club that evening, Dr. E. A. Strecker, of Philadelphia, was the principal speaker.

BOOKS — WAR VICTIMS

During the war, the libraries of half the world were destroyed in the fires of battle and in the fires of hate and fanaticism. Where they were spared physical damage, they were impoverished by isolation. There is an urgent need — now — for the printed materials that are basic to the reconstruction of devastated areas and that can help to remove the intellectual blackout of Europe and the Orient.

There is need for a pooling of resources and for co-ordinated action in order that the devastated libraries of the world may be restocked, so far as possible, with needed American publications. The American Book Center for War Devastated Libraries, Incorporated, has come into being to meet this need. It is a program that is born of the combined interests of library and educational organizations, of governmental agencies and of many other official and nonofficial bodies in the United States.

The American Book Center is collecting and is shipping abroad scholarly books and periodicals that will be useful in research and necessary in the physical, economic, social and industrial rehabilitation and reconstruction of Europe and the Far East.

The Center cannot purchase books and periodicals; it must depend on gifts from individuals, institutions and organizations. Each state will be organized to participate in the program through the leadership of a state chairman. Other chairmen will organize interest in the principal subject fields.

Co-operation with these leaders or direct individual contributions are welcomed.

What is needed. — Shipping facilities are precious and demand that all materials be carefully selected. Emphasis is placed on publications issued during the past decade, on scholarly books that are important contributions to their fields, on periodicals (even incomplete volumes) of significance and on fiction and nonfiction of distinction. All subjects — history, the social sciences, music, fine arts, literature and especially the sciences and technologies — are wanted.

What is not needed. — Textbooks, out-dated monographs, recreational reading, books for children and young people, light fiction, materials of purely local interest, popular magazines, such as *Time*, *Life*, *National Geographic* and so forth, and popular nonfiction of little enduring significance, such as Gunther's *Inside Europe*, Haliburton's *Royal Road to Romance* and so forth, should not be sent. Only carefully selected federal and local documents are needed, and donors are requested to write directly to the Center with regard to specific documents.

How to ship. — All shipments should be sent prepaid via the cheapest means of transportation to The American Book Center, c/o The Library of Congress, Washington 25, D. C. Although the Center hopes that donors will assume the costs of transportation of their materials to Washington, when this is not possible, reimbursements will be made on notification by card or letter of the amount due. The Center *cannot* accept material that is sent collect. Reimbursement cannot be made for packing or other charges beyond actual transportation. When possible, periodicals should be tied together by volume. It will be helpful if missing issues are noted on incomplete volumes.

CORRESPONDENCE

SCARLET FEVER OR STREPTOCOCCAL INFECTION?

To the Editor: Sing a dirge for scarlet fever — it will soon be as extinct (statistically) as the Dodo bird and the heath hen!

To be sure the quarantine period for the disease has been cut from six to three weeks in most places, but this three weeks out of a family's life, when a case of "streptococcus throat" (caused by the same strain of the same "bug") is not quarantined at all, is a useless sacrifice so far as controlling the spread of the disease is concerned. So why quarantine?

Despite the fact that recent advances have proved that we can, with the first few injections of penicillin, render the throat free from streptococci and practically prevent complications, the Blue Cross will only pay for hospitalization of its policyholders when they *have* complications! It will, however, pay without question for hospitalization of "hemolytic streptococcus throats with a toxic rash." (If there is one disease in which hospitalization is advisable to save life and prevent permanent crippling, it is scarlet fever — *all* patients should be able to get injections of penicillin every three hours for at *least* six days.)

Henceforth, *I* see no cases of scarlet fever. All my patients will have streptococcus throats with toxic rashes. No more quarantine penalties, no more "gypping" by the Blue Cross of *my* patients! How about yours? Statistics will prove, I am sure, that in a few years there is no such thing as scarlet fever!

It is another version of the old story of diphtheria. With the advent of antitoxin in England, antivivisectionists pointed out, quite correctly, that there was a sharp increase in the number of cases of diphtheria. They failed to mention, however, that there were *no* cases of laryngeal croup. The profession had been educated to call diphtheria "diphtheria!" Why not let us call streptococcal infections "streptococcal infections"?

PAUL R. WITHINGTON, M.D.

350 Randolph Avenue
Milton 86, Massachusetts

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held May 8, the Board voted to suspend the registration of Dr. Jean C. Marchand, 210 Lafayette Street, Salem, for six months because of gross misconduct in the practice of his profession as shown by violation of the Federal Narcotic Act.

H. QUIMBY GALLUPE, M.D., *Secretary*

State House
Boston

REPORT OF MEETING

MEDICAL LIBRARY ASSOCIATION

The Medical Library Association held its forty-fifth annual meeting in New Haven, Connecticut, on March 25, 26 and 27. Headquarters were at the Hotel Taft and sessions met in the Historical Library, Sterling Hall of Medicine, Yale University. The program featured reports on the Army Medical Library, a symposium entitled "International Co-operation" and addresses on the subjects "Training for Medical Librarianship" and "British Medical Libraries in Wartime."

The following officers were elected: president, Dr. Walton B. McDaniel, 2d, of the College of Physicians, Philadelphia; vice-president, Dr. C. Abbott Beling, of Newark, New Jersey; secretary, Miss Heath Babcock, of the New York State Medical Library, Albany, New York; and treasurer, Mr. Jurgen G. Raymond, of the New York Academy of Medicine, New York City.

It was voted to hold the 1947 convention in Cleveland, Ohio, the exact date to be determined later.

EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

The second regular meeting of the Eastern Association of Electroencephalographers was held on Friday, April 12, at the Postgraduate Club of the Institute of Living at Hartford, Connecticut, with thirty-six members present. A constitution and by-laws were adopted, creating a new office of vice-chairman, to which post Dr. Herbert H. Jasper, of the Neurological Institute of Montreal, was elected.

As chairman of the Liaison Committee, Dr. Hallowell Davis reported that the American Physiological Society had appointed Dr. Herbert H. Jasper and Dr. Frederick A. Gibbs to represent their society on the joint committee to review the problems of clinical electroencephalography and to consider appropriate action to promote a high standard of electroencephalography. The Council on Physical Medicine of the American Medical Association has also replied favorably to the memorandum of the Eastern Association of Electroencephalographers, with the American Neurological Association and the American Psychiatric Association both informally expressing favorable interest.

Dr. Milton H. Kibbe, of Springfield, Massachusetts, presented a paper describing experiences and findings in electroencephalography in an Army general hospital, with Dr. Charles E. Henry following with a corresponding paper based on Navy experience.

At the meeting on Friday, March 1, at the Institute of Living at Hartford, Connecticut, when the Eastern Association of Electroencephalographers was organized, Dr. Robert S. Schwab was elected chairman and Dr. Charles W. Stephenson was elected recorder.

NOTICES

ANNOUNCEMENTS

Dr. Louis Hermanson announces the removal of his office to 171 Bay State Road, Boston.

Dr. John A. Murphy announces the opening of an office at 47 Bay State Road, Boston, for the practice of gynecology and obstetrics.

Dr. Frederick P. Nadel, on termination of military service, is resuming the practice of medicine and surgery at 269 Harvard Street, Cambridge 39.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, June 6, at 7:15 p.m., in the classroom of the Nurses' Residence. Dr. Edwin B. Astwood will speak on the subject "Thiouracil in the Treatment of Hyperthyroidism." Dr. Merry Pittman will be chairman.

GRANTS AND FELLOWSHIPS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, announces that it will entertain applications for grants in cancer research to become effective July 1, 1947. Applications will be received until September 15, 1946. Applications for fellowships and senior fellowships in cancer research of the American Cancer Society for the ensuing year will be received until December 1, 1946.

To date the Committee on Growth has recommended to the American Cancer Society a total of seventy-five research grants and fourteen fellowships. The committee will continue to recommend support of research in the basic sciences and in clinical investigative medicine broadly pertaining to problems of growth. It will also continue to rely heavily for counsel on its advisory divisions of chemistry, biology, physics and clinical investigation and their subjacent panels in specialized areas of research.

Applications for research grants for the current year will no longer be entertained. Communications should be addressed to the Committee on Growth, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

NEW ENGLAND HEART ASSOCIATION

The annual meeting of the New England Heart Association will be held on Monday, June 3, in the Dowling Amphitheater of the Boston City Hospital at 8:15 p.m. The scientific program will be preceded by a short business meeting, including the election of officers for the ensuing year.

PROGRAM

Indications for Removal of Foreign Bodies from the Heart and the Technic of Cardiotomy. Dr. Dwight E. Harken.

Electrocardiographic Variations in Heart Trauma. Dr. Paul Zoll.

Discussion.

Interested physicians and medical students are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 30

FRIDAY, MAY 31

*9:00–10:00 a.m. The Role of Infection in Shock. Dr. Joseph C. Aub. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, JUNE 3

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, JUNE 4

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, JUNE 5

*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater, Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:30–4:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

MARCH 15–SEPTEMBER 15. Boston University Course for Discharged Medical Officers. Page 240, issue of February 14.

APRIL 1–JUNE 1. Intensive Course in Ophthalmology. Page 240, issue of February 14.

MAY 29. New England Obstetrical and Gynecological Society. Page 616, issue of May 2.

JUNE 3. New England Heart Association. Notice above.

JUNE 6. New England Hospital for Women and Children. Notice above.

JUNE 20–22. American Association for the Study of Goiter. Page 312, issue of February 28.

JUNE 29. American College of Chest Physicians. Page 544, issue of April 18.

JULY 3. Harvard Medical Alumni Association. Page 682, issue of May 16.

SEPTEMBER 4–7. American Congress of Physical Medicine. Page 616, issue of May 2.

OCTOBER 7–18. New York Academy of Medicine. Page 544, issue of April 18.